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المجلة الصحية لشرق المتوسط

La Revue de Santé de la Méditerranée orientale

The World Health Organization Regional Office for Eastern Mediterranean Region adopted the Healthy Cities Programme in 1990, as a dynamic movement and a multi-sectoral platform, to facilitate commitment at the highest political level to formulate a common vision with a focus on public health development involving all stakeholders, including the civil society.

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المجلة الصحية لشرق المتوسط

هى المجلة الرسمية التى تصدر عن المكتب الإقليمى لشرق المتوسط بمنظمة الصحة العالمية. وهى منبر لتقديم السياسات والمبادرات الجديدة في الصحة العامة والخدمات الصحية والترويج لها، ولتبادل الآراء والمفاهيم والمعطيات الوبائية ونتائج الأبحاث وغير ذلك من المعلومات، وخاصة ما يتعلق منها بإقليم شرق المتوسط. وهى موجهة إلى كل أعضاء المهن الصحية، والكليات الطبية وسائر المعاهد التعليمية، وكذا المنظمات غير الحكومية المعنية، والمراكز المتعاونة مع منظمة الصحة العالمية والأفراد المهتمين بالصحة فى الإقليم وخارجه.

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EST une revue de santé officielle publiée par le Bureau régional de l'Organisation mondiale de la Santé pour la Méditerranée orientale. Elle offre une tribune pour la présentation et la promotion de nouvelles politiques et initiatives dans le domaine de la santé publique et des services de santé ainsi qu'à l'échange d'idées, de concepts, de données épidémiologiques, de résultats de recherches et d'autres informations, se rapportant plus particulièrement à la Région de la Méditerranée orientale. Elle s'adresse à tous les professionnels de la santé, aux membres des instituts médicaux et autres instituts de formation médico-sanitaire, aux ONG, Centres collaborateurs de l'OMS et personnes concernés au sein et hors de la Région.

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Healthy Cities Programme in the Eastern Mediterranean Region: concurrent progress and future prospects

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Urbanization has been rapidly increasing during the past two decades and it is estimated that by 2030, two thirds of the world's population would be living in urban areas (*1*), exposing the population to a large number of environmental, social, cultural, economic and behavioural factors that impact population health and wellbeing (*2*).

In response to such challenges, the Healthy Cities concept was instigated in 1977 that, along with the Alma Ata Declaration and commitment of countries at the Thirtieth World Health Assembly in Geneva, Switzerland (*3*), would empower communities to lead socially and economically productive lives. A number of policy documents from the World Health Organization (WHO) and other bodies suggested introducing new approaches to managing cities and addressing health challenges, focusing more on health determinants and prevention than medical interventions (*4*).

In 1984, the idea of Healthy Cities was discussed at the "Beyond Health Care" conference in Toronto, Canada, where emphasis on promoting community participation and inter-sectoral action was advocated, in order to resolve city-wide issues in a holistic manner. As the Healthy City concept was widely accepted globally and had been established in all six WHO Regions, WHO launched the Healthy Cities Programme in 1986 as a long-term international initiative to place health high on the local political agenda, and to engage the international community in promoting the health and well-being of city dwellers through the collaborative efforts of the public, private, voluntary and community sectors (*5*).

This paradigm shift towards a more integrated approach to health has grown over the last few decades. Accordingly, the WHO Regional Office for Eastern Mediterranean Region (WHO/EMRO) adopted the Healthy Cities Programme in 1990, as a dynamic movement and a multi-sectoral platform, to facilitate commitment at the highest political level to formulate a common vision with a focus on public health development involving all stakeholders, including the civil society.

The Eastern Mediterranean Region (EMR) Healthy Cities Programme started in the Islamic Republic of Iran and then expanded to 12 other countries (Afghanistan, Bahrain, Egypt, Jordan, Kuwait, Lebanon, Morocco, Oman, Pakistan, Saudi Arabia, Sudan and United Arab of Emirates) with different implementation phases. WHO/EMRO continued to provide technical support to its Member States to assess and prioritize their needs and develop their plans of action.

Currently, the Healthy Cities Programme receives WHO support for multi-sectoral collaboration, enhancing community participation, improving public health among EMR populations towards achieving the Sustainable development Goals-2030 (SDG-2030), Universal Health Coverage (UHC) in line with WHO's 13th General Programme of Work (GPW13) 2019–2023 (*6*). In addition, the Healthy Cities Programme promotes community empowerment and enhances community participation in assessment of needs and effective planning in line with the WHO/EMRO Regional Director's Vision 2023 "Health for All by All" (*7*).

Since the implementation of the Healthy Cities Programme entails innovative actions addressing health determinants, WHO/EMRO developed guidelines for programme implementation. This incorporated 80 indicators under 9 domains in line with social determinants of health (SDH) and SDGs, including: community organization/mobilization for health development; intersectoral collaboration; availability of information; environmental health; health development; education and literacy; skill development and capacity building; microcredit activities; and emergency preparedness and response (*7*). Other WHO regions are looking to adapt these indicators within their own context in order to have a unified path for global Healthy Cities Programme implementation.

To facilitate networking and experience exchange, WHO/EMRO established the Regional Healthy Cities Network (RHCN) during 2012, which also offers an interactive website (*8*). Currently, 77 cities have joined the RHCN with a population of over 22 million from 13 countries of the Region. Sharjah (United Arab Emirates) was the first city to be officially recognized by WHO/EMRO as a "Healthy City" in 2015, followed by five cities in Saudi Arabia and one city each in Bahrain, Kuwait and Oman during 2018–2019. More EMR cities are ready for evaluation, currently performed by WHO and external

experts against the 80 indicators (referred to above), and awarded the title of "Healthy City" upon achieving at least 80 % of indicators. Awarded cities are re-evaluated every three years.

In spite of widespread acceptance of the Healthy Cities Programme, it still faces various challenges due to different reasons including: lack of institutionalization of the Healthy Cities Programme's concepts and methodologies as integral parts of health and development sectors; lack of documentation and evidence building at the local level; focus of health information systems mainly on morbidity and mortality data, rather than including disaggregated equity and SDH indicators; and insufficient partnership with potential partners such as nongovernmental organizations, donors, UN agencies, academic and research institutions.

Currently, the Healthy Cities Programme is one the highest priorities of WHO's agenda in the Region for 2019, and is managed within WHO/EMRO in its new division of Healthier Populations (after being hosted within the division of health systems followed by division information, evidence and research), with plans for close collaboration with other WHO divisions, technical programmes, and specialized environmental protection agencies, considering its cross-cutting nature. To scale up the programme in the EMR, focus is being directed at fostering its resources; strengthening its governance, leadership and management structure; building evidence for informed policy-making with regards to health and wellbeing; using the programme as a platform to promote health and improve prevention; early detection and management of public health problems; enhancing community/civil society empowerment in needs assessment and programme implementation; establishing RHCN networking with other regional networks; and reviewing/updating Healthy Cities Programme indicators to align with SDGs and GPW13.

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Prevalence, control and risk factors related to hypertension among Moroccan adults: a multicentre study

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Abstract

Background: Hypertension is a leading risk factor for mortality and morbidity.

Aims: The objective of this study was to determine the prevalence and clinical profile of hypertension in a large sample of individuals in Morocco.

Methods: This was a multicentre and cross-sectional study conducted on patients consulting primary care physicians in Morocco between 2008 and 2009. Data were collected via a medical examination and a questionnaire covering patient demographics, medical history and cardiovascular risk factors.

Results: In total, 10 714 individuals attending primary care physicians participated in this study. Mean age was 49.6 ± 16.3 years. The total prevalence of hypertension was 39.8%. When adjusted for age and sex, the overall prevalence of hypertension was 26.6% (26.3% in men and 28.0% in women). Among patients with history of hypertension, 85.9% of patients were prescribed antihypertensive medication and/or lifestyle and dietary advice. Nevertheless, only 17.1% had controlled hypertension.

Conclusions: This study suggests that the prevalence of hypertension in Morocco is high. Hypertension may also be underdiagnosed and ineffectively treated. Efforts to heighten public awareness and control of hypertension should be enhanced in the public primary care services.

Keywords: hypertension, Morocco, epidemiology, antihypertensive, controlled hypertension.

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Introduction

Most low- and middle-income countries are currently confronting a significant public health challenge due to a continued high burden of communicable diseases and noncommunicable diseases, especially hypertension (*1–3*). Elevated blood pressure (BP) represents the principle contributor to the global mortality of disease and burden (*4*). Globally, elevated BP is the leading risk factor for mortality and morbidity, accounting for 7% [CI 95%, 6.2–7.7] of global disability adjusted life years and 9.4% [CI 95%, 8.6–10.1] million deaths in 2010 (*5*). Also, the number of individuals with uncontrolled hypertension (defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) increased from 605 to 978 million because of population growth and aging (*5*). The number of adults with hypertension in 2025 was predicted to increase by about 60% to a total of 1.56 billion globally (*6*).

Hypertension may be present for many years before it becomes an emergency. Many patients around the world continue to have unrecognized or untreated hypertension, with variation between countries (*7*). The JNC 7 report "Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure", showed that hypertension was unrecognized in 30% of cases; in recognized patients, 54% were treated and only 34% were controlled (*8*).

In Morocco, the ministry of health conducted a study on the main cardiovascular risk factors in 2000 and indicated that the prevalence of hypertension in adults was 33.6% (*9*). In North Africa a cross-sectional study ETHNA (Epidemiological Trial of Hypertension in North Africa) was conducted in 28 500 patients consulting primary care physicians in Algeria, Tunisia and Morocco; the total prevalence of hypertension was 45.4% (*10*). The aim of this study was to determine the prevalence and clinical profile of hypertension in a large sample of individuals in Morocco.

Methods

Participants

This was a national, multicentre, epidemiological, cross-sectional study conducted in patients attending primary care physicians in Morocco between September 2008 and January 2009. Eligible patients were aged 18 years or older of either sex who were willing to participate in the survey. Patients who had fever (≥ 38°C) were excluded from the study (*11*).

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was reviewed by the Independent Ethics Committee.

The sample size was calculated based on an estimated prevalence of hypertension of 30%. With a risk of error of 0.01 (1%), a difference of imprecision of 1.0%, and a cluster effect of 2, the number to be included in the study was rounded to 11 000. A cluster was defined as a neighbourhood in an urban area and a locality in a rural area. One cluster was selected at random from each region included in the survey and one primary care centre from each commune of the cluster was selected at random. One hundred and ten physicians participated in the study, each of which recruited more than 100 participants.

Data collection and medical examination

Data were collected by participating primary care physicians using a checklist that covered demographics of the patient; personal and family medical history; risk factors for cardiovascular disease and hypertension; and whether a BP measurement had been recorded in the last year. If the patient had a history of hypertension, additional information from their medical history was collected including duration of hypertension; prescription of antihypertensive medication (including type(s), number of medications, any single-pill combinations); and history of hypertension-related complications (including left ventricular hypertrophy, angina, myocardial infarction, chronic heart failure, stroke, chronic kidney disease, retinopathy, revascularization or peripheral arterial disease).

Patients were also clinically examined and measurements were taken for weight, height, waist circumference and BP. Two BP measurements were planned: one after 5 minutes of rest and the second following a further 2-minute rest after the completion of the first measurement. When possible, BP measurements were recorded as the mean of the two measurements. Hypertension was identified according to the criteria of the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) guidelines (*12*): grade 1 hypertension, SBP 140–159 mmHg and/or DBP 90–99 mmHg; grade 2 hypertension, SBP 160–179 mmHg and/or DBP 100–109 mmHg; grade 3 hypertension, SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg; systolic hypertension (also known as isolated systolic hypertension) was graded (1, 2 or 3) according to the SBP values in the above ranges, provided that DBP was < 90mmHg.

Current smoker was defined as a person who continued to smoke at the time of survey daily or occasionally and ex-smoker was defined as a person who had quit smoking. Abdominal obesity was defined as a waist circumference ≥ 90 cm in men and waist circumference ≥ 80 cm in women. Body mass index (BMI) was computed as weight (kg)/height (m^2) and classified according to the World Health Organization criteria as overweight (BMI ≥ 25 kg/m^2) and obese (BMI ≥ 30 kg/m^2). Diabetes, hypercholesterolaemia, kidney failure and postmenopausal women are self-reported from patients.

Statistical methods

Initially, descriptive analyses were used to determine the crude prevalence of hypertension over the whole sample. In addition, age- and sex-adjusted rates were calculated by multiplying the age- and sex-specific rate for each age group in the study population by the appropriate weights from a standard population (*13*). The overall age- and sex-adjusted rates were the sum of these products.

The associations between various facets of hypertension (e.g. a history of hypertension, newly detected hypertension, hypertension severity, controlled hypertension) and patient demographics and personal medical profile (e.g. age, sex, personal and family medical history, body mass index (BMI), smoking and current treatment) were investigated. Statistical analyses were based on conventional parametric tests (χ^2 test, Student's *t*-test and analysis of variance). A test was considered significant when $P < 0.05$. Where comparisons are made within a category containing more than two subcategories, *P* values have been denoted 'within category'. Statistical analyses were performed using SPSS (version 17.0).

Results

Participants

In this study, through 110 general physicians, 10 714 pas tients were included. Table 1 presents the characteristics of the study population. The mean age of participants was 49.6 ± 16.3 years. Two thirds of the participants were female (66.7%) and 73.4% of participants lived in urban area. Almost 43.5% of participants were illiterate, and 12.1% were educated to university graduate level. The mean BMI of the participants was 25.9 ± 4.8 kg/m^2. Only 12.4% of patients consulted primary care for cardiovascular motif.

Risk factors

Table 2 presents an overview of risk factors of hypertension in the study population. Family history of abdominal obesity, hypercholesterolaemia and type 2 diabetes were present in 35.6%, 13.5% and 13% of patients respectively. Menopause was present in 41.2% of female participants. Near half (46%) of participants had a normal BMI, and almost 52% of participants were overweight or obese. Smoking was present in 25.5% of males and 1.8% of females.

Table 1: Sociodemographic characteristics of the study population

	Number	%
Age (n=10 552)		
Mean ± SD: 49.6 ± 16.3 years		
18–29	1924	18.2
30–39	1948	18.5
40–49	2130	20.2
50–59	1968	18.7
≥ 60	2582	24.5
Sex (n=10 598)		
Female	7069	66.7
Area of habitation (n=10 303)		
Rural	2736	26.6
Urban	7567	73.4
Education (n=10 331)		
Illiterate	4495	43.5
Elementary school	1927	18.7
Secondary school	2654	25.7
University graduate	1255	12.1

SD = standard deviation.

Table 2: Hypertension risk factors in the overall study population

	Number	% (CI 95%)
Smoking		
Male (n= 3484)		
Ex-smoker	561	16.1 (14.8–17.3)
Current smoker	889	25.5 (24.1–26.9)
Female (n= 6925)		
Ex-smoker	52	0.8 (0.6–1.1)
Current smoker	123	1.8 (1.5–2.1)
Abdominal obesity (n=9972)	3550	35.6 (34.7–36.4)
Diabetes (n=10 663)		
Type 1	295	2.8 (2.5–3.1)
Type 2	1388	13.0 (12.3–13.7)
Hypercholesterolemia (n=10 064)	1358	13.5 (12.8–14.2)
Kidney failure (n=10 029)	140	1.4 (1.2–1.6)
Postmenopausal women (n=6730)	2771	41.2 (40.0–42.4)
HRT in postmenopausal women (n=2452)	84	3.5 (2.8–4.3)
Body mass index (BMI)		
Underweight (< 18.5 Kg/cm^2)	261	2.5 (2.2–2.9)
Normal (18.50–24.99 Kg/cm^2)	4728	45.7 (44.6–46.7)
Overweight (25–29.99 Kg/cm^2)	3398	32.8 (31.9–33.8)
Obesity		
Classe I (30–34.99 Kg/cm^2)	1510	14.6 (13.9-15.3)
Classe II (35–39.99 Kg/cm^2)	361	3.5 (3.2–3.8)
Classe III (≥ 40 Kg/cm^2)	87	0.8 (0.7–1.0)

HRT = hormone replacement therapy

CI = Confidence interval

Prevalence of hypertension

Among the 10 717 participants surveyed, 4262 individuals had hypertension – an overall crude prevalence of 39.8% [95% CI 38.9–40.8]. Of these individuals, 2480 (58.2%) had a history of hypertension. Among them, 2130 (85.9%) received antihypertensive medication. When adjusted for age and sex, the overall prevalence of hypertension was 26.6% (95% CI 25.8–27.4; 26.3% in men [95% CI 24.8–27.8] and 28.0% in women [95% CI 26.9–29.1]). The duration of hypertension in patients with a history of hypertension averaged 7.6 ± 5.7 years. In near half of the patients (48.5%), the duration of hypertension was more than 5 years.

An overview of hypertension severity in patients with a history of hypertension is shown in Table 3. In total, 7.2% of patients had either normal or optimal BP at the time of the study visit. Around 10% of the patients had normal–high BP and around 33% of the patients had isolated systolic hypertension. Of patients who were untreated, approximately 20% and 18% had hypertension grade 1 and grade 2, respectively. More than half (51.6%) of patients had isolated systolic hypertension.

The proportions of patients with a history of hypertension according to their socio-demographic characteristics are summarized in Table 4. The proportions of patients with hypertension increased with age ($P < 0.0001$); 53.4% of participants aged 60 years or older had a history of hypertension, compared with just 1.6% of those aged 18 to < 30 years. Hypertension was more common in women than men (24.4% vs 22.2%; $P = 0.01$), in rural than in urban areas (26.4% vs 22.9%; $P < 0.005$), in illiterate participants than in those with some formal education (e.g. 33.8% for illiterate vs 12.6% for university graduates; $P < 0.0001$ within category). Hypertension was more common in individuals who had abdominal obesity, diabetes, hypercholesterolaemia and kidney failure than in individuals without these comorbidities (all $P < 0.001$). Hypertension was also more common in individuals who were overweight or obese than in those who were of normal weight or underweight ($P < 0.001$ within category).

Control of hypertension

Among patients with a history of hypertension, 85.9% of patients were prescribed antihypertensive medication and or lifestyle and dietary advice. Nevertheless, only 17.1% had controlled hypertension (BP < 140/90 mmHg). Control of disease was higher in patients who received antihypertensive medication: 18.4% in treated patients versus 9.1% in untreated patients.

Table 3: **Severity of hypertension in study population**

	Patients with history of hypertension			Newly detected (n=1782)
	Received treatment (n= 2130)	Untreated (n = 350)	Total (n=2480)	
	%	%	%	%
Hypertension classes				
Optimal	0.8	0.6	0.8	–
Normal	7.0	2.6	6.4	–
High normal	10.5	6.0	9.9	–
Hypertension grade 1	10.8	9.7	10.6	19.6
Hypertension grade 2	19.0	22.6	19.5	18.4
Hypertension grade 3	18.3	22.6	18.9	10.4
Isolated systolic hypertension	32.7	34.3	32.9	51.6
Grade 1	54.8	50.0	54.1	69.6
Grade 2	34.4	31.7	34.0	23.4
Grade 3	10.8	18.3	11.9	7.1
Invalid measurements	0.8	1.7	1.0	–
Total	**100.0**	**100.0**	**100.0**	**100.0**

The proportions of patients with controlled hypertension according to their socio-demographic characteristics are shown in Table 5. Controlled hypertension was not associated with gender. However it was higher in university graduates than in patients educated to lower levels (P = 0.006 within category). It was also higher in younger patients, urban area and low weight patients (P < 0.001).

Newly detected hypertension

Among the 8047 participants surveyed without a history of hypertension, 1782 (22.1%) individuals had hypertension at consultation. Of these individuals, 18.4% and 10.4% had hypertension grade 2 and 3 respectively. The proportions of patients with newly detected hypertension according to their socio-demographic characteristics are summarized in Table 6. The frequency of newly detected hypertension increased significantly with age (P < 0.001). Newly detected hypertension was also higher in illiterate people than in those with a formal education (P < 0.001 within category) and in people from rural areas than in those from urban areas (P < 0.001). The prevalence of newly detected hypertension increased with BMI (P < 0.001). Therefore, in obese patients' grade 3, the proportion of hypertension was 43.8% versus 16.7% in patients with normal BMI.

Discussion

The ETHNA study is the first cross-sectional study with a large sample in the Maghreb. This study in Morocco shows that the prevalence of hypertension is high in the population consulting general medicine (overall prevalence = 39.8%; age-adjusted prevalence = 26.6%) and its treatment and control were still inadequate. Among these individuals with hypertension at consultation, 58.2% had a history of hypertension. In addition, when comparing Morocco to other countries of North Africa, Morocco had the lowest prevalence of hypertension among adults ≥ 18 years compared to Tunisia (47.4%) (*14*) and Algeria (49.5%) (unpublished data). This study showed also a rising overall prevalence of hypertension compared to the study of ministry of health in 2000 that indicates that the prevalence of hypertension in adults is 33.6% (*9*). Urbanization, sedentary lifestyle, high consumption of salt and fatty food may have contributed to the rising prevalence of hypertension (*15,16*).

In Arab countries, hypertension prevalence varied widely between and within countries (*17*). The prevalence of hypertension ranged from 20.1% in the Syrian Arab Republic (*18*) to 50.2% in Algeria (*19*), while within countries, the prevalence varied from 35.3% to 50.2% in Algeria (*19,20*). For national studies, hypertension prevalence ranged from 27.6% in Palestine (*21*) to 41.5% in Oman (*22*). In the Iranian population, the prevalence of hypertension ranged from 18.4% (*23*) and 38% (*23*). Risk factors for hypertension in Eastern Mediterranean Region (EMR) countries consist of two categories: non-modifiable risk factors including age, sex, genetic factors and family history of hypertension, and modifiable factors such as physical inactivity, obesity, high levels of dietary sodium intake, hypercholesterolaemia, diabetes and educational level (*15–26*).

In treated patients, the control of hypertension decreases the risk of cardiovascular events. Despite the treatment rate observed in our study the control of hypertension was lower. However, national and international surveys suggest that many people continue to have unrecognized or untreated hypertension (*13,27*). Consequently, efforts to heighten public awareness and control should be enhanced in the public primary care services where majority of the hypertensive individuals are managed.

Table 4: Proportions of individuals with a history of hypertension according to socio-demographic and clinical characteristics

Category	Number of individuals in overall study population	Individuals with history of hypertension (%)	*P*
Age (years)			**<0.0001**
18–30	1877	1.6	
30–40	1904	4.8	
40–50	2096	16.1	
50–60	1946	32.3	
≥ 60	2547	53.4	
Sex			**0.013**
Female	6942	24.4	
Male	3479	22.2	
Origine			**<0.001**
Rural	2686	26.4	
Urban	7443	22.9	
Education level			**<0.0001**
Illiterate	4421	33.8	
Elementary school	1901	20.3	
Secondary school	2611	14.1	
University graduate	1233	12.6	
Smoking			**0.18**
Ex-smoker or smoker	1612	24.9	
Not smoker	8721	23.3	
Abdominal obesity			**<0.001**
Yes	3498	36.4	
No	6314	16.7	
Diabetes			**<0.001**
No diabetes	8819	17.7	
Type 1	286	57.7	
Type 2	1376	53.3	
Hypercholesterolemia			**<0.001**
Yes	1344	62.4	
No	8562	17.3	
Postmenopausal women			**<0.001**
Yes	2745	46.2	
No	3874	09.0	
Kidney failure			**<0.001**
Yes	140	75.7	
No	9734	22.4	
Body mass index classes			**<0.001**
Underweight	252	14.3	
Normal	4655	15.9	
Overweight	3356	25.5	
Obesity			
Classe I	1486	37.5	
Classe II	359	42.9	
Classe III	87	46.0	

Table 5: Hypertension control rates in patients with history of hypertension according to socio-demographic characteristics

	Number of patients in population	Patients with controlled hypertension (%)	*P*
Age (years)			**0.003**
18–30	30	40.0	
30–40	92	31.5	
40–50	338	15.4	
50–60	628	17.4	
≥ 60	1361	16.0	
Sex			**0.84**
Female	1695	17.1	
Male	772	17.4	
Area of habitation			**0.001**
Rural	709	12.4	
Urban	1708	18.7	
Education			**0.006**
Illiterate	1496	15.2	
Elementary school	386	17.6	
Secondary school	366	18.9	
University graduate	155	28.8	
Body mass index classes			**<0.001**
Underweight	36	25.0	
Normal	738	22.5	
Overweight	856	17.3	
Obesity			
Classe I	556	11.2	
Classe II	154	13.0	
Classe III	40	12.5	

Table 6: Prevalence of newly detected hypertension in individuals without a history of hypertension according to sociodemographic characteristics

	Number of individuals in population	Individuals with newly detected hypertension (%)	*P*
Age (years)			**<0.001**
18–30	1847	04.7	
30–40	1812	11.2	
40–50	1758	23.0	
50–60	1318	37.3	
≥ 60	1189	46.8	
Sex			**0.012**
Female	5247	21.2	
Male	2705	24.3	
Area of habitation			**<0.001**
Rural	1977	28.0	
Urban	5735	20.4	
Education			**<0.001**
Illiterate	2925	31.1	
Elementary school	1515	20.2	
Secondary school	2245	16.3	

Table 6: Prevalence of newly detected hypertension in individuals without a history of hypertension according to sociodemographic characteristics (*concluded*)

University graduate	1078	12.9	
Body mass index classes			**<0.001**
Underweight	216	10.2	
Normal	3917	16.4	
Overweight	2500	25.1	
Obesity			
Classe I	930	35.2	
Classe II	205	42.4	
Classe III	47	42.6	

The study shows that a minority of patients had controlled hypertension and the determinants of uncontrolled disease were older patients, illiterate individuals and obese patients. The WHO SAGE study, realized in middle-income countries, showed that hypertension control rates are particularly low for adult across distinct cultures (*28*). Similarly, many studies showed, as demonstrated in the ETHNA study, that several determinants influence the control of BP like age, gender, area of habitation and BMI. In the FLAHS study (*29*), a survey conducted in metropolitan France, the determinants of BP control are age (55–64 years vs 80 years old; 57.6%/49.1%), gender (women vs men; 60.3%/50.1%), BMI (< 25 vs > 30; 63.1%/46.1%). With regards to factors associated with hypertension control, in the REDISCOVER study (*30*), residing in the rural areas and being female were identified as the independent factors. Poor BP control is linked to other factors related to physician or patient, i.e. lack of adherence to treatment, comorbidity, depression and high salt intake (*31*).

Our results confirms that hypertension prevalence was high among individuals from rural area compared to urban area, based on data collected by the ministry of health in 2000 (*32*). A recent meta-analysis study showed that prevalence estimates of hypertension were higher in urban communities, compared to participants in rural settings in Latin America, Asia and Sub-Saharan Africa (*33*). However, in Europe and central Asia the relationship was similar to our findings but there was no difference between rural and urban areas in the Middle East and North Africa region (*33*). Possible explanations for this phenomenon include the fact that epidemiologic and nutrition transition also affect people from rural regions. In rural areas, initiatives to change dietary behaviour should be implemented in order to reduce cardiovascular risk factors, especially reducing salt intake (*34*).

This study had a number of limitations linked to their observational design and the fact that data are only collected from general practitioners. Results of BP may be affected by the environment and the instrument of measurement. In addition, BP of individuals fluctuates through the time. Therefore, a confirmation of hypertension is required by a qualified person and on a different day. Overall, the above limitations are quite common in all studies of this nature and are unlikely to have a significant impact on the overall hypertension prevalence, especially considering the large sample size. In addition, comparisons with other studies are possible because of adjustment of hypertension prevalence on age and sex.

Conclusion

This study indicates that hypertension is highly prevalent and may be ineffectively managed in Morocco. Efforts to heighten public awareness and control of hypertension should be enhanced in the public primary care services.

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Competing interests: None declared.

Prévalence et contrôle de l'hypertension et facteurs de risque associés chez les adultes marocains : étude multicentrique

Résumé

Contexte : L'hypertension est un facteur de risque de mortalité et de morbidité principal.

Objectifs : La présente étude a pour objectifs de déterminer la prévalence et le profil clinique de l'hypertension dans un vaste échantillon d'individus au Maroc.

Méthodes : Il s'agit d'une étude multicentrique transversale menée auprès de patients consultant des médecins de soins primaires au Maroc entre 2008 et 2009. Les données ont été recueillies au moyen d'un examen médical et d'un questionnaire portant sur la démographie des patients, les antécédents médicaux et les facteurs de risque cardio-vasculaire.

Résultats : Au total, 10 714 médecins de soins primaires ont participé à cette étude. L'âge moyen était de 49,6 ± 16,3 ans. La prévalence totale de l'hypertension était de 39,8 %. Après ajustement selon l'âge et le sexe, la prévalence de l'hypertension était de 26,6 % (26,3 % chez les hommes et 28,0 % chez les femmes). Parmi les patients ayant des antécédents d'hypertension, 85,9 % des patients se sont vu prescrire des antihypertenseurs et/ou ont reçu des conseils concernant le mode de vie et le régime alimentaire. Néanmoins, seulement 17,1 % d'entre eux présentaient une hypertension contrôlée.

Conclusions : Cette étude suggère que la prévalence de l'hypertension au Maroc est élevée. L'hypertension peut également être sous-diagnostiquée et traitée de manière inefficace. Les efforts visant à sensibiliser davantage le public et à mieux contrôler l'hypertension devraient être intensifiés dans les services de soins primaires publics.

معدل انتشار ارتفاع ضغط الدم ومكافحته وعوامل الخطر المتعلقة به بين البالغين المغاربة: دراسة متعددة المراكز

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الخلاصة

الخلفية: يعد ارتفاع ضغط الدم أحد عوامل الخطر البارزة التي تسبب الوفاة والمراضة.

الأهداف: هدفت هذه الدراسة إلى تحديد معدل انتشار ارتفاع ضغط الدم ومرتسمه السريري في عينة كبيرة من الأفراد في المغرب.

طرق البحث: أُجريت هذه الدراسة المقطعية والمتعددة المراكز على المرضى الذين يراجعون الأطباء على مستوى الرعاية الأولية في المغرب بين عامي ٢٠٠٨ و٢٠٠٩. تم جمع البيانات من خلال فحص طبي واستبيان يغطي المحددات السكانية للمرضى وتاريخهم المرضي وعوامل الخطر ذات الصلة بأمراض القلب والأوعية الدموية.

النتائج: إجمالاً، شارك ١٠٧١٤ شخصًا قاموا بمراجعة الأطباء على مستوى الرعاية الأولية في هذه الدراسة. وبلغ متوسط العمر ١٦,٣ ± ٤٩,٦ عامًا. وبلغ إجمالي معدل انتشار ارتفاع ضغط الدم ٣٩,٨٪. وعند ضبط المعدل مع الأخذ في الاعتبار العمر ونوع الجنس، بلغ إجمالي معدل انتشار ضغط الدم ٢٦,٣٪ (٢٦,٦٪ بين الرجال و٢٨,٠٪ بين النساء). ومن بين المرضى الذين يوجد في تاريخهم المرضي إصابة بارتفاع ضغط الدم، ٨٥,٩٪ من المرضى وُصِفَت لهم أدوية مضادة لارتفاع ضغط الدم و/ أو نصائح تتعلق بأسلوب الحياة ونظام التغذية. ومع ذلك، وُجد أن ١٧,١٪ فقط من المرضى لديهم ارتفاع ضغط الدم تحت السيطرة.

الاستنتاجات: تشير هذه الدراسة إلى أن معدل انتشار ارتفاع ضغط الدم في المغرب مرتفع. وقد لا يُشخَّص ارتفاع ضغط الدم ولا يُعالج بشكل جيد وفعّال. ويجب بذل الجهود لإذكاء وعي الجمهور بشأن ارتفاع ضغط الدم وتعزيز مكافحته في خدمات الرعاية الأولية المقدمة بالقطاع العام.

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Outcome of heat stroke patients referred to a tertiary hospital in Pakistan: a retrospective study

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Abstract

Background: Climate change has heightened the threat of heat stroke in previously temperate zones.

Aims: This study aimed to assess the outcome of patients in relation to mortality and the role of effect modifiers among heatstroke patients presenting to a tertiary care hospital in Karachi during June 2015.

Methods: A retrospective observational study was conducted on heatstroke patients 20–27 June 2015 at the Emergency Room(ER) of a private hospital in Karachi, Pakistan. Patients' demographic data, disease severity, presentation and outcomes were determined. Statistical data was reported as numbers, percentages and mean ± SD.

Results: In total, 315 patients reported to ER; 76.6% patients survived, 23% expired. Males were 55% and 60% patients were fully mobile. Hypertension was the most frequent concurrent disorder. Fever documented in 79.4% and CNS derangement in 73.3% patients were the top most presenting features. Fever and disease severity were found to exert significant impact on disease outcome. Mortality rate dropped from 26 June onwards from 24.35% to 15.9% by using evaporative cooling technique combined with air conduction and maintaining room temperature at 22–24°C.

Conclusions: Poor outcome during heatstroke can be minimized by advance planning and timely intervention in low- and middle-income countries.

Keywords: heatstroke, mortality, morbidity, climate change, Pakistan

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Introduction

Climate change has contributed to a paradigm shift in the lives of people with more episodes of heat-related illnesses being recorded and an average temperature increase of 0.8°C has been noted since the 20th century (*1–3*). In June 2015, the Islamic Republic of Iran was hit by a severe heat wave, believed to be the second highest with a recorded temperature high of 74°C, with an actual air temperature of 46°C and a high dew point temperature of 32°C (*3*). Both India and Pakistan endured major loses during that period, with fatalities reported to be 1400 and 1300 respectively (*5,6*). Karachi is a heavily populated city and suffered significantly due to a high heat index, urban island effect, frequent power breakdowns and dehydration as citizens were fasting during the Islamic Holy Month of Ramadan. The emergency departments of all major hospitals dealt with the majority of patients presenting with varying degrees of heat illness.

Heat stroke is a life-threatening illness characterized by an elevated core body temperature above 40°C and central nervous system dysfunction that results in delirium, convulsions or coma (*4*). During heat waves, major risk factors for heat stroke include heat exposure, high ambient temperatures, solar radiation, urban heat island effect, poor constitution, extremes of age, isolation and poor access to air conditioning (*5*). It is also relatively common among persons with chronic mental disorders or cardiopulmonary diseases and those receiving medications that interfere with salt and water balance, such as diuretics, anti-cholinergic agents, and tranquilizers that impair sweating (*6*). Heat stroke is a result of the failure of the body to regulate its temperature accordingly along with a severe acute-phase response that culminates in release of heat-shock proteins (*7*). This results in multi-organ damage caused by the cytotoxic effect of the heat compounded by the inflammatory and coagulation responses of the host.

Heat-related illness includes a variety of disorders; heat stroke, heat exhaustion, heat cramps and heat rashes. Based on pathophysiology, Yashuka et al. have introduced a grading system to assess severity of heat illness (*8*). Grade I includes mild cases with heat cramps or syncope. Grade III is the presence of any one of the following three conditions; brain dysfunction, liver/kidney dysfunction, and disseminated intravascular coagulation (DIC) based on clinical examination and laboratory data. Grade II includes patients not fulfilling Grades I and III criteria.

Early reduction of body core temperature is the key to manage heatstroke, although no single established optimal cooling method is available. Different treatment modalities, both invasive and non-invasive, based on the principles of evaporation, conduction and convection are used for rapid heat dissipation before irreversible organ damage occurs. Some of these techniques include specialized cooling bed units, cold water immersion, cold blankets, and cold packs over neck, groin and axilla, wetting the body along with continuous fanning and the use of the muscle relaxant dentrolene (*9*).

In the summer of 2015, Karachi was severely affected by a heat wave during which the peak air temperature recorded was 44.8°C (*10*). Heat Index is a commonly used parameter based on relative humidity and maximum air temperatures to gauge what the temperature feels like. A heat index of more than 51.66°C is very likely to cause heat stroke (*11*). In Karachi the heat index reached 66.1°C and 58.3°C on 20 June and 22 June 2015, resulting in a high patient influx to emergency departments and associated mortalities (*10*). This retrospective study is based on the clinical profiles, the outcome of patients in terms of survival and the role of effect modifiers on mortality among heatstroke patients who presented to the emergency room (ER) during 20–27 June 2015 at a tertiary care hospital in Karachi.

Methods

A retrospective study using non-random consecutive sampling was carried out at the emergency and haematology departments of Liaquat National Hospital, Karachi during 20–27 June 2015. Patients with heat illness other than heat stroke, brought dead to ER or having incomplete medical records were excluded as per study plan (Figure 1). All patients with heat stroke who reported to ER during the study period had their demographic data, clinical presentation, medical and drug history assessed. Severity of disease was graded using Yashuka et al. grading system as discussed (*8*). Glasgow Coma Scale (GCS) was used to determine neurological status; a score of 15–12 was considered as mildly impaired and between 11–9 as moderately impaired. Coma was defined as a score of 8–3 (*12*). Mobility was assessed using Knaus Chronic Health status Score and stratified into four groups as follows: Class A) normal health status; Class B) moderate activity limitation; Class C) severe activity limitation due to chronic disease; and Class D) bedridden patient (*13*). Evaporative cooling is defined as spraying water over the patient and facilitating evaporation and convection with the use of fans (*9*). This technique was implemented from 26 June onwards. Outcome of the study was ER or in-hospital mortality versus those surviving to discharge. Effect modifiers between survivors and non-survivors were compared.

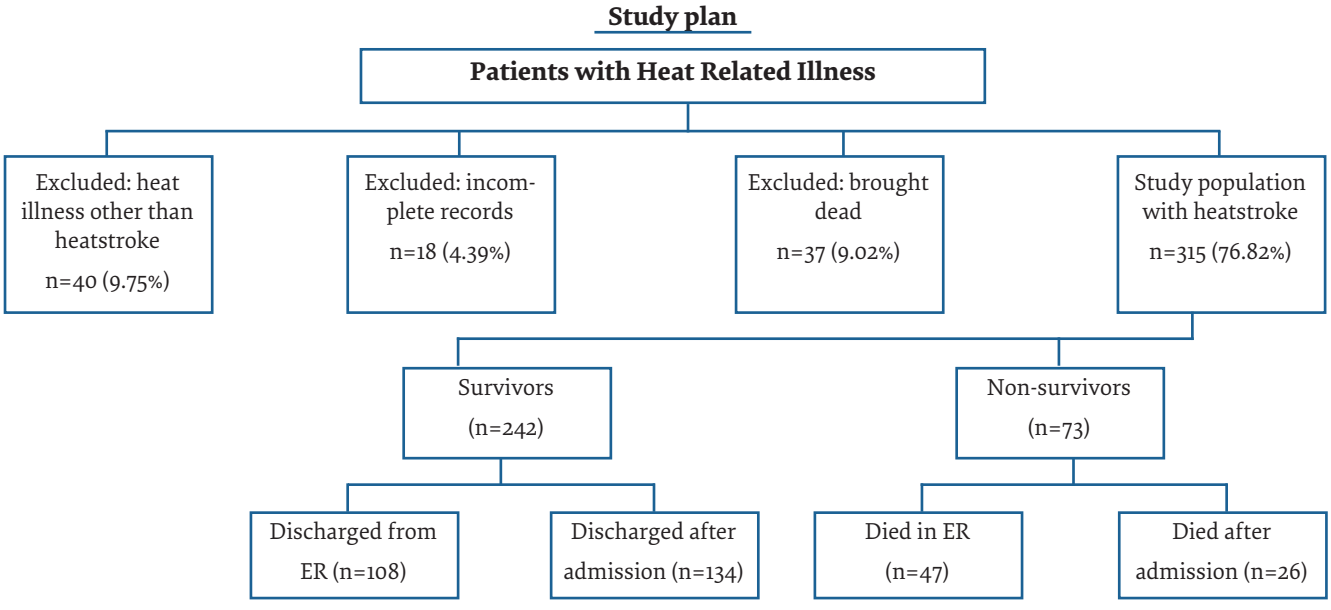
Statistical analysis

Data was analyzed by using Statistical Package for Social Sciences (SPSS) version 21. Mean and standard deviation were computed for quantitative variable and frequency and percentage were calculated for qualitative variables. Stratification was done with regards to qualitative variables to see the effect of these modifiers on study groups by using Chi Square test and Fisher's exact test. Differences in quantitative variables were compared by using Independent *t*-test. *P* value of ≤ 0.05 was considered as significant.

Ethical considerations

This study was conducted after approval from the Research and Ethics Committee of Liaquat National Hospital, Karachi, Pakistan.

Figure 1: Study plan of June 2015 patients with heat-related illness



Results

A total of 315 patients (172 [54.6%] males and 143 [45.4%] females) with heatstroke were included in the study to assess the clinical presentation and disease outcome. For the study period the maximum air temperature ranged from 37–44.8°C with highest attendance of 159 patients recorded on 22 June, 2015 (10). The relationship of hospital visits and patient outcome is shown in Figure 2. The mean age of the study population was 58.87 ± 17.68 years (range: 1–95). Mean GCS score was 12.03 ± 4.22 (range: 3–15). Majority of patients (n=208, 66%) had normal mobility. Most common concurrent disease present in 176 (55.9%) patients was hypertension. Fever was the most frequent complaint seen in 250 (79.4%) patients. The mean body temperature documented on presentation was 37.9 ± 1.44°C (range:36.1–41.1) with high fevers of 39.4°C or above recorded in 69 patients of which 19 expired in ER. Central nervous system (CNS) disturbances were seen in 231 (73.3%) patients with 70 (22.2%) patients presenting in a comatose state (GCS < 8); out of 315 patients, 242 (76.8%) survived. Detailed characteristics for heatstroke patients are presented in Table 1.

Demographic features such as age groups and gender were almost similar between survivors and non-survivors. The mean age of survived patients was 58.55 ± 17.55 years while mean age was 59.94 ± 18.19 years for non-survivors. A significant association of survival status was found with fever (P = 0.045) and disease severity (P = < 0.001). Detailed association and mean comparisons are presented in Table 2.

Discussion

Heatstroke occurs in epidemic form during heat waves, and both hospital emergency department visits and intensive care unit (ICU) admissions increase sharply more so during first seasonal heat waves (*14–16*). Consecutive days of heat exposure, even among a heat-acclimated population can increase mortality risk (*17,18*); low- and middle-income countries are more vulnerable to these adverse effects (*19*). The lives of the poor in many hot countries are already compromised by routine summer heat. Extrapolating this to the global thermal environment projected in future decades gives a scenario where their situation will deteriorate and increasingly, other countries will begin to experience these oppressive climatic conditions.

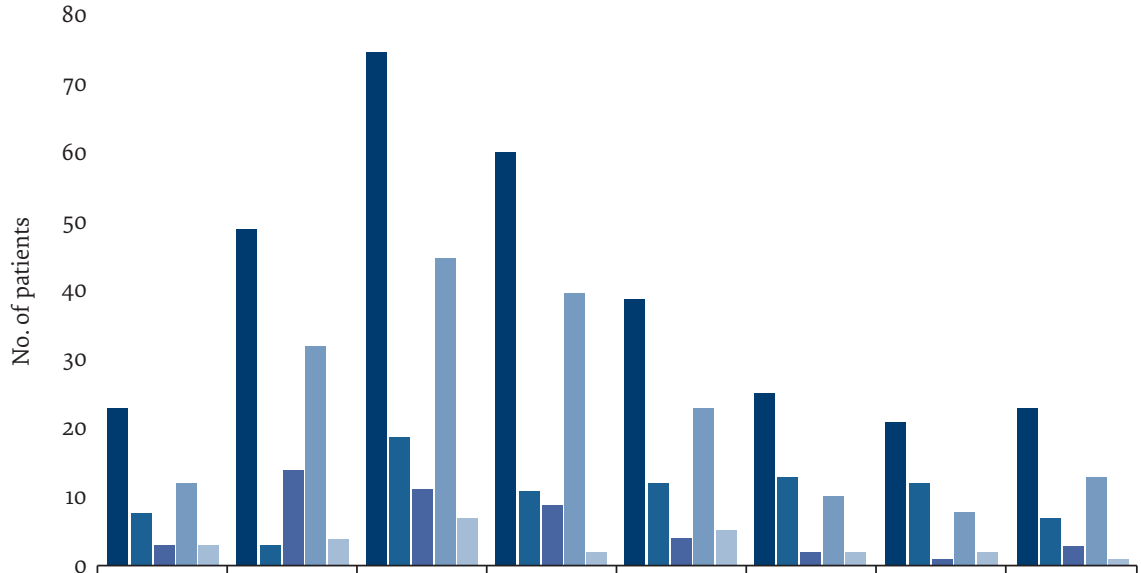
Findings in our report indicate a mortality of 23% from heat stroke, while 33% was reported by Mohnasalven et al., although their sample size was limited to 15 patients (*20*). Current studies, now based on relative changes in all-cause mortality during heat stroke show an upward trend when compared to previous years (*21*). Non-work related heat illness is more common among the older population (*22,23*). Our data differ slightly as the mean age of heat stroke patients was close to 60 years with 18 patients aged less than 25 years. This difference can be attributed to the confounding effect of exertional heat stroke cases inadvertently included in the study.

Comparisons between males and females show a high but non-significant increase in mortality among females in this study, which concurs with other studies based on non-exertional heat stroke data (*24*). We found hypertension and not diabetes mellitus as the leading associated disease in this study, although the latter is known as a strong effect modifier for mortality among heat stroke patients due to impairment of the autonomic control and endothelial function in diabetic patients. (*25–27*). Contrary to the fact that drugs such as thiazide diuretics, vasoconstrictors and beta blockers affect the thermo-regulation by decreasing body's ability to shunt large volumes of blood away from the centre to dissipate heat, no significant association was found between long-term drug use and mortality among our study

Table 1: Characteristics of heat stroke patients

Variable	N (%)
Sex	
Male	172(54.6)
Female	143(45.4)
Mobility status	
Class A	208(66)
Class B	46(14.6)
Class C	41(13)
Class D	20(6.3)
Co-morbidities	
Hypertension	176(55.9)
Diabetes Mellitus	112(35.6)
Ischemic Heart Disease	53(16.8)
Others	27(8.6)
None	94(29.8)
Long-term medications	
None	159(50.5)
Anti-hypertensive drugs	125(39.7)
Oral Hypoglycemic drugs	79(25.1)
Diuretics	33(10.5)
Others	28(8.9)
Clinical presentation	
Fever	250(79.4)
CNS Symptoms	231(73.3)
Shortness of breath/ palpitations	104(33)
Dehydration	55(17.5)
Others	2(0.6)
Disease severity	
Grade I	106(33.7)
Grade II	93(29.5)
Grade III	116(36.8)
Status	
Survivors	242(76.8)
Non survivors	73(23.2)

Figure 2: Emergency department visits for June 2015 heatstroke patients with outcome



	20.06.15	21.06.15	22.06.15	23.06.15	24.06.15	25.06.15	26.06.15	27.06.15
Patients with heat stroke	23	49	75	60	39	25	21	23
Discharged from *ER	8	3	19	11	12	13	12	7
Expired in *ER	3	14	11	9	4	2	1	3
Admitted	12	32	45	40	23	10	8	13
Expired post admission	3	4	7	2	5	2	2	1

*Emergency room

Table 2: Comparison between survivor and non-survivor heat stroke patients

Characteristics	n (%)		*P-value*
	Survivors	Non-survivors	
Age (years)			
<25 years	14(5.8)	4(5.5)	>0.99
26-50 years	60(24.8)	18(24.7)	
>50 years	168(69.4)	51(69.9)	
Mean ±SD°	58.55±17.55	59.94±18.19	0.557
Sex			
Male	139(57.4)	33(45.2)	0.066
Female	103(42.6)	40(54.8)	
Co-morbidities			
None	76(31.4)	18(24.7)	0.269
Hypertension	137(56.6)	39(53.4)	0.631
Diabetes mellitus	84(34.7)	28(38.4)	0.568
Ischemic heart disease	41(16.9)	12(16.4)	0.92
Others	19(7.9)	8(11)	0.406
Long-term medications			
None	122(50.4)	37(50.7)	0.968
Anti-hypertensive drugs	100(41.3)	25(34.2)	0.279
Oral hypoglycemic drugs	59(24.4)	20(27.4)	0.602
Diuretics	28(11.6)	5(6.8)	0.248
Others	24(9.9)	4(5.5)	0.243

Table 2: Comparison between survivor and non-survivor heat stroke patients (*concluded*)

Characteristics	n (%)		*P-value*
	Survivors	Non-survivors	
Clinical presentation			
Fever	187(76.9)	63(87.7)	<0.05
CNS symptoms	173(71.5)	58(79.5)	0.177
Shortness of breath/palpitations	83(34.3)	21(28.8)	0.378
Dehydration	41(61.9)	14(19.2)	0.659
Others	2(0.8)	0(0)	>0.99
Mobility status			
Class A	164(67.8)	44(60.3)	0.066
Class B	38(15.7)	8(11)	
Class C	29(12)	12(16.4)	
Class D	11(4.5)	9(12.3)	
Disease severity			
Grade I	105(43.4)	1(1.4)	<0.001
Grade II	56(23.1)	37(50.7)	
Grade III	81(33.5)	35(47.9)	
GCS score			
12-15	168(69.4)	41(56.2)	0.095
9-11	24(9.9)	12(16.4)	
3-8	50(20.7)	20(27.4)	
Mean ±SD°	12.28±4.12	11.19±4.47	0.052

Chi-Square and Fisher Exact test applied

°Independent t-test applied.

population. Another common parameter that failed to leave its mark on mortality in this report was restricted mobility, although it was close to be significant at *P* value of 0.066. The above mentioned discrepant results hint at major differences in dynamics between high-income and low- and middle-income countries.

We found history of fever and disease severity at presentation as the only significant risk factors for death in this study. Patients with fever and severe disease manifestations are inclined to have low GCS score and a high risk of mortality, hence a poor outcome (*28*,*29*). Initially high mortality rates occurred in the ER in the first four days, since the public and healthcare providers were unprepared for the adverse climatic conditions. Patients were managed in ER using random cooling methods and irregular intravenous fluid administration. Three days later specific measures were implemented that included evaporative cooling combined with air conduction with installation of pedestal fans, maintaining room temperature at 22–24°C, rigorous hydration with intravenous fluids and designating four ICUs exclusively for managing these patients. These measures brought down the mortality rate from 24.35% to 15.9%, which was equivalent to a 35% reduction. The Evaporative conduction cooling technique was adapted since it is considered an effective cooling mechanism at high ambient temperatures, is well tolerated by elderly patients, and is more suitable for classic heat strokes in epidemic situations due to ease of application and access (*9*).

Despite climate change related risks of heatstroke, there is a temporal trend for a decline in mortality, which can be due to easy access to healthcare, change in age structure and resilience to warm climate over time (*30*). Ahmadabad in the state of Gujarat implemented its "Heat Action Plan" in 2013 and hence suffered fewer deaths than cities without heat plans during the May 2015 heat wave (*31*). We saw a high mortality during the one week period due to lack of a heat health action plan as well as a heat health warning system on a national level and a lack of preparedness on a local level.

A single centre study such as this may not be enough to depict an overall picture; nevertheless, our results have implications for the future. Further studies should consider the socioeconomic and infrastructural issues of heat-sensitive population groups in order to better manage heat-related illnesses in future.

Conclusion

This study of health data during the June 2015 heat wave in Karachi saw an upsurge in mortality and morbidity during the peak heat wave period, with a decline after introducing appropriate measures. Fever and disease severity were found to exert a significant impact on disease

outcomes. Old age, comorbid conditions, medications and restricted mobility had no significant influence on mortality.

Limitations

This study has a number of limitations due to its retrospective nature; patterns of external or internal heat exposure were not documented and thus made it difficult to differentiate between exertional and non-exertional heat stroke. Patients' socioeconomic status was not evaluated, which could have helped in understanding the demographics of heat-related illnesses. In addition, being a retrospective study the response to the cooling measures applied (assessed by fall in body temperature per minute) was not recorded. Like any observational study, our results may be subject to confounding bias.

Recommendations

To prevent possible rapid increases in mortality in future due to changing climatic conditions, it is recommended to develop a heat wave response plan that can be implemented in a timely manner. Additional prospective studies examining heat-related morbidity and quantifiable response to management are necessary for health risk assessments.

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Résultats pour les patients victimes d'un coup de chaleur orientés vers un hôpital tertiaire au Pakistan : étude rétrospective

Résumé

Contexte : Le changement climatique a accru la menace de survenue des coups de chaleur dans les régions auparavant tempérées.

Objectifs : La présente étude avait pour but d'évaluer les résultats pour les patients en termes de mortalité et le rôle des modificateurs d'effet chez les patients victimes d'un coup de chaleur se présentant dans un hôpital de soins tertiaires à Karachi en juin 2015.

Méthodes : Une étude d'observation rétrospective a été menée sur des patients victimes d'un coup de chaleur du 20 au 27 juin 2015 aux services des urgences d'un hôpital privé à Karachi, au Pakistan. Les données démographiques des patients, la sévérité des troubles, leur présentation et les résultats ont été déterminés. Les données statistiques ont été présentées sous forme de nombres, de pourcentages et d'écart-type ± moyen.

Résultats : Au total, 315 patients se sont présentés aux services des urgences ; 76,6 % des patients ont survécu et 23 % sont décédés. Les patients étaient des hommes pour 55 % et 60 % des patients étaient tout à fait capables de bouger. L'hypertension était le trouble concomitant le plus fréquent. La fièvre documentée chez 79,4 % des patients et les troubles du système nerveux central chez 73,3 % d'entre eux étaient les caractéristiques les plus fréquentes. On a constaté que la fièvre et la gravité des troubles avaient un impact significatif sur l'issue de l'événement. Le taux de mortalité est passé de 24,35 % à 15,9 % à partir du 26 juin grâce à l'utilisation de la technique du refroidissement par évaporation combinée à la conduction de l'air et au maintien de la température ambiante à 22-24 °C.

Conclusions : Les mauvais résultats enregistrés pendant un coup de chaleur peuvent être minimisés par une planification préalable et une intervention en temps opportun dans les pays à revenu faible ou intermédiaire.

المخرجات الصحية للمرضى المصابين بضربة الحرارة المُحالين إلى أحد مستشفيات الرعاية الثالثية في باكستان: دراسة استرجاعية

شستة تبسم، نايلة رزة، سيد زبير شاه

الخلاصة

الخلفية: أدى تغير المناخ إلى تزايد خطر الإصابة بضربة الحرارة في المناطق التي كان مناخها معتدلاً في السابق.

الأهداف: هدفت هذه الدراسة إلى تقييم المخرجات الصحية للمرضى فيما يتعلق بالوفاة ودور معدِّلات الأثر بين المرضى المصابين بضربة الحرارة الذين يأتون إلى أحد مستشفيات الرعاية الثالثية في مدينة كراتشي خلال شهر يونيو/ حزيران ٢٠١٥.

طرق البحث: أُجريت دراسة مشاهدة استرجاعية على المرضى المصابين بضربة الحرارة في الفترة بين ٢٠ و٢٧ يونيو/ حزيران ٢٠١٥ في غرفة الطوارئ التابعة لأحد المستشفيات الخاصة في مدينة كراتشي، باكستان. وتم تحديد البيانات السكانية للمرضى وشدة مرضهم وأعراض المرض والمخرجات الصحية الخاصة بهم. وتم إعداد البيانات الإحصائية في شكل أرقام ونسب مئوية ومتوسط ± الانحراف المعياري.

النتائج: إجمالاً، أُبلغ عن قدوم ٣١٥ مريضًا إلى غرفة الطوارئ حيث نجا ٧٦,٦٪ من المرضى، بينما توفى ٢٣٪. وكان ٥٥٪ من الذكور و٦٠٪ من المرضى قادرين تمامًا على التحرك. وكان ارتفاع ضغط الدم هو الاضطراب المصاحب الأكثر تكرارًا. وكانت الإصابة بالحمى في ٧٩,٤٪ من المرضى واختلال الجهاز العصبي المركزي في ٧٣,٣٪ منهم أكثر الأعراض ظهورًا. كما وُجدَ أن الحمى وشدة المرض يؤثران بشكل كبير على مخرجات المرض. وانخفض معدل الوفاة ابتداءً من يوم ٢٦ يونيو/ حزيران فما بعد من ٣٥,٢٤٪ إلى ٩,١٥٪ باستخدام أسلوب التبريد البخري المصاحب للتوصيل الهوائي والحفاظ على درجة حرارة الغرفة عند ٢٢–٢٤ درجة مئوية.

الاستنتاجات: يمكن الحدّ من المخرجات الصحية الضعيفة عند الإصابة بضربة الحرارة من خلال التخطيط المسبق والتدخل في الوقت المناسب في البلدان منخفضة ومتوسطة الدخل.

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Obesity and maternal perception: a cross-sectional study of children aged 6 to 8 years in Kuwait

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Abstract

Background: Childhood obesity is on the increase in the Middle East.

Aims: This study aimed to determine the prevalence of obesity in those aged six to eight years and to investigate maternal perception of child weight.

Methods: A nation-wide study of data on height and weight were obtained from nurses' records, and maternal perceptions were assessed through a self-administered questionnaire. Sample size comprised 2208 individuals with BMI measurements and 1002 with BMI and maternal perception data.

Results: The prevalence of overweight and obese children combined was 40.9% as per WHO cut-off values and 39.7% as per Centres for Disease Control and Prevention categorizations. We also found that 77.9% of overweight and 45.4% of obese children were perceived by their mothers to have healthy body weights. Additionally, 39.8% of children with normal weight were also judged by their mothers to be underweight.

Conclusions: An alarmingly high prevalence of childhood obesity among Kuwaiti children, coupled with mothers distorted perception of their child's actual weight status is a serious concern that requires urgent public health intervention.

Keywords: obesity, maternal perception, body image, children, Kuwait

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Introduction

Globally, the number of adults with a body-mass index (BMI) of 25 kg/m^2 or greater has increased between 1980 and 2013 from 28·8% to 36·9% in men, and from 29·8% to 38·0% in women (*1*). This rise is particularly important because obesity has been linked to many illnesses including cardiovascular diseases, diabetes and hypertension. Adults are not the only victims of the rapid increase in the obesity epidemic; children and adolescents are falling victims as well. According to the World Health Organization (WHO), the number of overweight or obese infants and young children under the age of five years increased from 32 million globally in 1990 to 42 million in 2013 (*2*).

Childhood obesity is a very serious problem, yet dangerously under-recognized (*3*). It was found that childhood obesity is a predictor of obesity and metabolic disorder in adulthood (*4*); therefore, it is of vital importance to control adult obesity at the root. According to Friedemann et al. (*5*) obese children share the same increase in risk as adults in developing comorbidities, such as hypertension, diabetes, and dyslipidemia. They are also more likely to develop psychosocial disorders as well as low self-esteem. (*6*)

The cause of childhood obesity is multifactorial. It includes behavioural factors, such as low levels of physical activity, poor nutrition, as well as environmental factors (*7–9*). It has also been noted that gestational diabetes and an early cessation or a complete lack of breastfeeding can increase the risk of developing obesity in children (*10,11*). Genetic factors have also been implicated as studies suggest that familial transmission of adiposity can reach up to 50% (*12*).

A factor often overlooked, but which nevertheless plays a definitive role in children's weight, eating habits and physical activity, is maternal perception of overweight and obesity and its influences (*13*). A number of studies have compared mothers' assessment of their child's weight with the child's body mass index (BMI). These studies concluded that as few as 32% and as many as 90% of mothers underestimate their children's weight as De La O et al. (*14*) summarized in their study. This demonstrates that there is a discrepancy between mother's perception and actual weight status of their children, which gives rise to the question: If mothers are not able to identify their child's obesity, how will they realize that the home environment they are creating is inadvertently unhealthy?

Obesity has most notably demonstrated an exponential increase in the Middle East, and in Kuwait there is a marked increase in the prevalence of childhood obesity (*1,15*). There is a longstanding cultural norm among the Kuwaiti population that "a fat baby is a healthy baby". In our study, we aimed to explore the maternal perception of the child's current BMI status and estimate the prevalence of childhood obesity in Kuwait.

Methods

A nationwide cross-sectional study was conducted in Kuwaiti public schools with a sample size of 2253 children using a multi-stage, gender-stratified randomized cluster-sampling scheme. There are 214 elementary public schools distributed across all six governorates in Kuwait, which are all unisex (i.e. all-male or all-female only). A list of schools compiled in the Ministry of Education website (http://www.moe.edu.kw) was used to sample the schools from all parts of Kuwait, both urban and semi-urban. The stratified multi-stage sampling scheme was conducted by first selecting the schools according to governorate and sex after assigning each school a number and then including all the classes as the second stage in this study, since we aimed to include all eligible students in each of the selected schools as clusters in our sampling scheme.

The schools to be included in this survey were randomly selected using an online random number generator (http://www.random.org). We selected one all-male and one all-female school randomly from each of the six governorates to be included in this study, resulting in a total of 12 schools included in this study. In these randomly selected schools all students aged 6 to 8 years and in grades one to three were included in this study as a cluster sample. We excluded students above the age of 8 years to rule out the effect of puberty. Also, choosing 6 years and above makes it more convenient because the average age of students starting primary school is 6 years in Kuwait. Data were obtained from nurse's records of height and weight and perception were assessed through a self-administered questionnaire.

Research instrument for the study consisted of two major parts.

Part A: Anthropometric data

Height and weight measured within three months prior to the date of data collection were obtained from nurses' records in school with the approval of the Ministry of Health. The nurses were trained to use the standardized scales issued by the Ministry of Health.

Part B: Maternal questionnaire

A 29-item questionnaire was employed in this study, in which mothers are mainly asked to classify their perception of their children's weight in a written form using a five point Likert scale ranging from "extremely underweight" to "extremely overweight". Maternal perception questions that were used in this study were based on validated tools used by previous researchers. (*14*,*16*)

Other items included were as follows:

1. Demographic and socioeconomic variables: age, nationality, occupation, education, income, and marital status.
2. Questions regarding the child: date of birth, birth weight, sibling number, birth order, breastfeeding and length of breastfeeding, and child comorbidities.
3. Questions regarding maternal perception: mothers and grandparents' perceptions.
4. Questions regarding child's nutrition and physical activity: amount of meals, type of food consumed, types of physical activity, video game and TV time.
5. Maternal anthropometry: mother's height and weight, self-perception of their body weight.

Sample size determination

As the main aim of this study was to evaluate the maternal perception associated with child overweight and obesity status, we computed the sample size required for an odds ratio (OR) of 1.5 or greater to be statistically significant. We found a sample size of 1151 would be sufficient for any OR of 1.5 or greater to be statistically significant at an alpha level of 5% with a power of 90%. However, based on previous studies, we estimated that the response rate from the mothers would not exceed 50%. This meant we would have to approach at least 2302 children to have 1151 sample required. We also computed that with the sample size of 1151, we could quantify the 95% confidence interval of the prevalence of obesity and overweight to be in the range of ± 4%. We used PASS12 to compute the sample size required (*17*).

Statistical analysis

Data were analysed using SPSS for Windows (version 23) (*18*). Based on the date of birth of the child, ages were calculated as well as the BMI of the children using their anthropometry data. Using Centres for Disease Control and Prevention (CDC) (*19*) and WHO age and gender specific cut-offs for BMI (*20*), the children were classified as underweight (< 5th percentile), normal (≥ 5th to < 85th percentile), overweight (≥ 85th to < 95th percentile), and obese (≥ 95th percentile). We used two cut-off points so that results can be interpreted in different meta-analysis studies that use either CDC or WHO (Table 1). For the prevalence of each BMI category, 95% confidence interval (CI) was also calculated. All bivariate and multivariate analyses used the CDC based classification in this study. This study utilized a multi-stage sampling scheme and as such intra-class correlations (ICC) of BMI of children nested within schools were computed to assess if the data could be analysed without taking the cluster structure into consideration.

Statistical analyses focused on comparing the child's BMI category with their mother's perception about their child's weight status (from extremely underweight to extremely overweight). In the univariate analysis, chi-square (for nominal variables) and chi-square for trend (for ordinal variables) were used to test if there was any statistically significant association between maternal underestimation (versus correct estimation) of their child's weight status and maternal characteristics. Underweight children were excluded from this analysis since their weight cannot be further underestimated. In addition, multivariate logistic regression with stepwise variable method was employed to assess which of the

Table 1: Age and sex specific cut-offs for BMI of children classified according to Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO)

Percentile	CDC						WHO					
	Boys			Girls			Boys			Girls		
	Age						Age					
	6	7	8	6	7	8	6	7	8	6	7	8
5th	13.7	13.7	13.7	13.4	13.4	13.5	13.4	13.6	13.8	13.1	13.2	13.4
85th	17.0	17.4	17.9	17.0	17.6	18.3	16.9	17.3	17.7	17.2	17.6	18.1
95th	18.4	19.1	20.0	18.8	19.6	20.6	18.0	18.5	19.1	18.6	19.1	19.8

maternal characteristics were independently associated with their underestimation.

Ethical approval

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Faculty of Medicine Ethics Committee in Kuwait University and the Ministry of Education and the Ministry of Health of Kuwait. Written informed consent was obtained from all subjects.

Results

The total number of elementary school students enrolled in the schools randomly selected for this study in Kuwait was 2553. Of this, complete anthropometric data were available on 2253 children. After restricting the age to those between 6 to 8 year olds, the sample size reduced to 2208 (831 males and 1377 females). Thus, 86% of all children in the study population were included in the analyses for the calculation of obesity prevalence. However, the response rate of the maternal perception survey was only 39% despite repeated reminders.

A total of 1002 records with complete BMI data on children were linked to their maternal perception data. In order to ascertain if the lack of participation was not associated with the child's BMI levels, the weight status of children whom mothers participated were compared against those who did not; there were no statistically significant differences between the child's weight statuses of participating mothers compared to those that did not participate (P = 0.747). ICC for BMI was 0.06, −0.02 and 0.002 for those aged 6, 7 and 8 year olds, respectively. In our view, such lower ICC provides sufficient justification for the analyses of data at the individual child level, safely ignoring the nested structure by schools for the purpose of data analyses.

The prevalence of overweight and obese children combined was 40.9% as per WHO cut-off values and 39.7% as per CDC categorizations (Table 2). The differences in classification of the children based on WHO compared to CDC were minimal from a clinical point of view. The rest of the analyses were carried out based on WHO classifications.

The prevalence of obesity and overweight combined, among females was 41.5% (95% CI = 39.4–43.5), whereas it was 36.7% (95% CI = 34.6–38.7) among male children (P = 0.024). The main objective of this study was to assess maternal perception of their child's weight status, since it is hypothesized here that maternal attitude plays a major role in the body weight of young children in Kuwait, given that these younger children are under maternal control. Maternal perception and the child's actual weight status are summarized in Figure 1.

It is also hypothesized that those mothers who underestimate their child's BMI could be associated with their socio-demographic characteristics such as age, income, and educational levels as well as their own BMI. Although a number of socio-demographic variables such as age, nationality, income, occupational status and educational level were found to be associated with maternal underestimation in univariate analyses, a stepwise multivariate regression models showed only nationality to be independently associated with it (Table 3). For maternal underestimation, the outcome variable in these analyses were considered when the mothers thought that their child was of normal weight,

Table 2: Prevalence of childhood obesity, overweight and other weight statuses in study population (*n*=2208)

	CDC		WHO		*P*-value
	N	(%)	N	%	
Underweight	124	(5.6)	96	(4.3)	0.049
Normal	1207	(54.7)	1211	(54.8)	0.947
Overweight	335	(15.2)	297	(13.5)	0.107
Obese	542	(24.5)	604	(27.4)	0.028
Total	2208	100.0	2208	100.0	

Table 3: **Predictors associated with maternal underestimation of child's weight status**

Parental characteristics	Total N	Maternal underestimation (%)	P-value
Parental age			**0.018**
25–35	459	(50.1)	
36–45	355	(53.8)	
>45	76	(65.8)	
Nationality			**<0.001**
Kuwaiti	724	(50.4)	
Non-Kuwaiti	222	(64.4)	
Occupational status			**0.025**
Retired	40	(62.5)	
Never worked	292	(59.2)	
Currently working	616	(50.5)	
Educational status			**0.034**
Middle school or below	139	(59.0)	
High school	203	(56.7)	
Diploma	226	(54.9)	
University	351	(49.6)	
Marital status			**0.728**
Married	844	(53.6)	
Divorced	70	(55.7)	
Income			**0.055**
<500 KD[2]	62	(56.5)	
501–1000 KD	281	(58.7)	
1001–1500 KD	244	(52.9)	
1501–2000 KD	176	(46.6)	
>2000 KD	169	(52.1)	
Parents' weight status			**0.751**
Normal weight	191	(50.8)	
Overweight/Obese	491	(52.1)	
Variable	**Multivariate stepwise logistic regression[1] Parental underestimation**		**P-value**
Nationality			
Kuwaiti	0.5 (0.3–0.7)		0.002
Non-Kuwaiti	Reference		

[1] *All maternal characteristics listed in this table were included in the multivariate regression model and only nationality was retained by the stepwise selection process.*

[2] *KD = US$ 3.29*

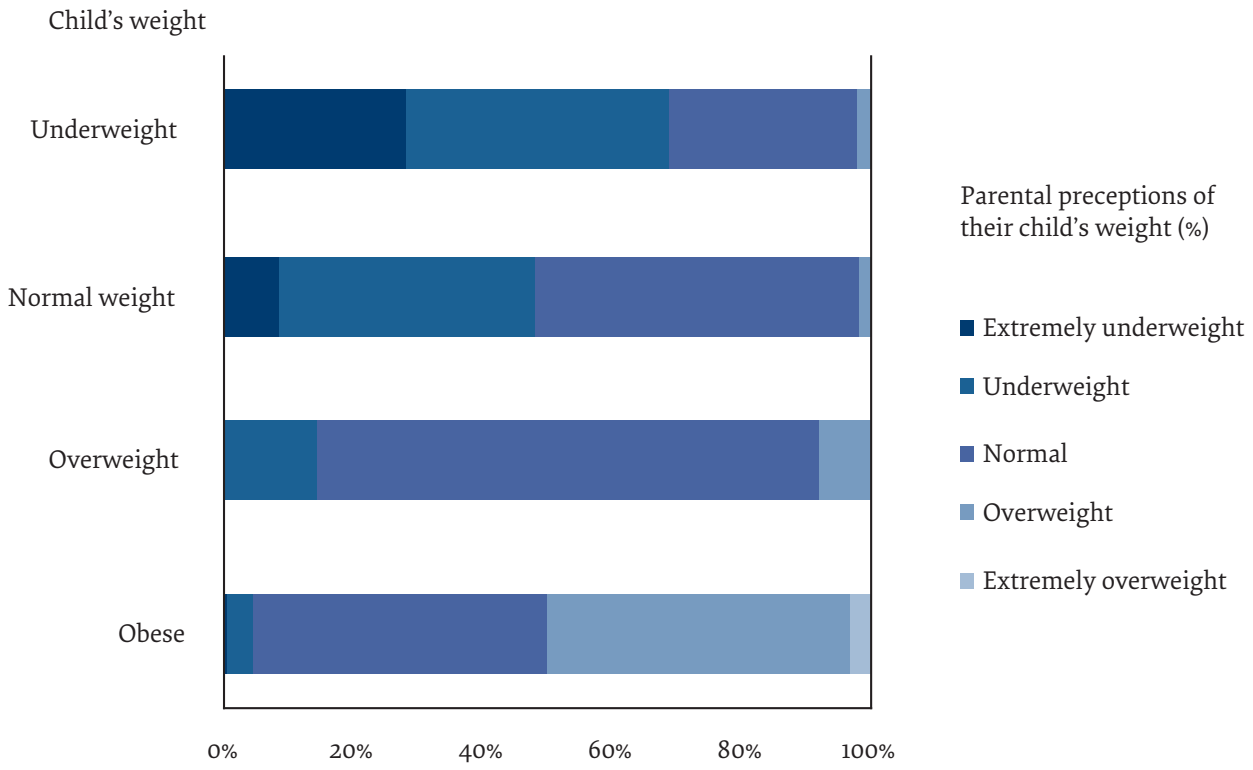
underweight, or extremely underweight, when in fact they were overweight/obese. If the child's weight status was normal and the mother felt that her child was underweight or extremely underweight was also taken to be underestimation.

Discussion

Kuwait has been described in the media as one of the most obese countries in the world (*21*). According to an earlier WHO report, Kuwait ranked as the 13th most obese country globally (*2,21*) and with regard to childhood obesity, Kuwait is also considered one of the highest ranking countries. In this study we found the prevalence of childhood overweight and obesity in children aged 6 to 8 years to be approximately 40%.

There is paucity of data on the prevalence of obesity among pre-pubertal children in the Gulf region. According to a former review article comparing childhood obesity among Middle Eastern countries (*22*), it was clear that Kuwait – in comparison with the prevalence determined in this study – was easily among the highest in terms of childhood obesity. However, published reports from other countries reported a considerably lower prevalence than 40%; for instance, the prevalence of childhood overweight and obesity in Germany was estimated to

Figure 1: Actual weight of the children versus the parental perception of their child's weight



be 18.3%, (23) and in France it was 15.2% (24). The higher prevalence noted in this study is alarming and demands research on the determinants of childhood obesity in Kuwait.

It is considered here that the child's sex might play a role in the development of overweight or obesity. Females appeared to be more overweight or obese (41.5%) than boys, which is similar to studies conducted in the United Arab Emirates, where it was found that the female population was more overweight or obese than male counterparts. (25) Moreover, studies conducted in the United States of America showed a similar pattern (1). This highlights the higher risk among females across different societies, regardless of demographic and cultural factors. At the level of adult obesity, more females appear to be obese in Kuwait (26). If childhood obesity is extrapolating into adulthood, then tackling it is tantamount to reducing the burden of disease that manifests in adulthood.

More importantly, our findings ascertained that the effect of parental perception is paramount to the body weight levels of children in Kuwait. Using a five-point Likert scale ranging from "extremely underweight", "underweight", "normal", "overweight", to "extremely overweight", we asked mothers to classify their perception of their child's weight. It became apparent that the rate of misperception on the mother's part exceeded that of any correct perception of their child's weight status. 92.2% of mothers with overweight children underestimated the true weight, with 77.9% considering them of normal weight and 14.3% underweight. Furthermore, 45.4% of mothers classified obese children as having normal weight and 4.0% as being underweight. It was also interesting to note that 39.8% of mothers also tended to consider their child to be underweight in spite of their child having normal weight (Figure 1). This supports suspicions that there appears to be an obvious distortion in Kuwaitis' perception of what constitutes a "healthy" physique.

Given that childhood obesity is linked to a plethora of diseases and is highly linked to the development of adult obesity, maternal perception can be used as a predictor of childhood obesity, as demonstrated in this study. Unfortunately, there is a paucity of studies related to this specific issue in Kuwait and the Gulf Arab region, which is experiencing higher level of obesity and related chronic diseases. The public health implications that can be addressed through the issue of maternal misperception and their active role in changing their child's weight status are innumerable. If we tackle childhood obesity at its root we can effectively reduce the rate of adult obesity with all its associated comorbidities such as heart disease, hypertension, and diabetes. This is vital as studies have quantified the risk of adult disease associated with obesity. For instance, the age-adjusted relative risk (RR (confidence interval [CI])) for cardiovascular disease increased among those who were obese in men (1.46 [1.20 –1.77]) and in women (1.64 [1.37–1.98]) (27).

Limitations

There are a number of limitations to this study that must be acknowledged. BMI is often criticized as an imperfect measure of adiposity, yet it is still one of the best meas-

ures available for population based assessments. Furthermore, the weight and height of the mothers as well as breast feeding history were all self-reported, with potential for a high risk of bias.

Conclusion

We found a very high prevalence (40%) of obesity and overweight in 6 to 8-year-old elementary school children in Kuwait, and 77.9% of overweight and 45.4% of obese children were perceived by their mothers to have normal body weights. Additionally, 39.8% of children with healthy body weight were judged by their mothers to be underweight. As such, we found that a large proportion of mothers underestimated their child's true weight status, which could negate all public health intervention on childhood obesity. If a mother misclassifies their overweight child as being of "healthy" or "normal weight" then it is expected that they will be hesitant to change their child's weight. For this reason, we believe that correct maternal perception is paramount to tackling the issue of childhood obesity. This can only be achieved by proving to mothers that their perception of a healthy weight is incorrect and this misperception may lead to chronic and negative health implications later in the child's life.

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Étude transversale de la perception maternelle de l'obésité des enfants âgés de 6 à 8 ans au Koweït

Résumé

Contexte : L'obésité de l'enfant est en augmentation au Moyen-Orient.

Objectifs : La présente étude visait à déterminer la prévalence de l'obésité chez les enfants de six à huit ans et à étudier la perception du poids des enfants par les mères.

Méthodes : Une étude nationale des données concernant la taille et le poids a été réalisée à partir des dossiers des infirmières et les perceptions des mères ont été évaluées au moyen d'un questionnaire auto-administré. La taille de l'échantillon comprenait 2208 personnes ayant des mesures de l'indice de masse corporelle (IMC) et 1002 sujets ayant des données sur l'IMC et la perception des mères.

Résultats : La prévalence combinée du surpoids et de l'obésité de l'enfant était de 40,9 % selon les valeurs seuils de l'OMS et de 39,7 % selon les catégories établies par les Centers for Disease Control and Prevention (CDC). Nous avons également constaté que 77,9 % des enfants en surpoids et 45,4 % des enfants obèses étaient perçus par leur mère comme ayant un poids corporel normal. De plus, 39,8 % des enfants ayant un poids normal ont également été jugés par leur mère comme ayant un poids insuffisant.

Conclusions : La prévalence alarmante de l'obésité infantile chez les enfants koweïtiens, associée à la perception déformée par les mères de l'état pondéral réel de leur enfant, est une préoccupation grave qui nécessite une intervention de santé publique urgente.

السمنة وإدراك الأمهات: دراسة مقطعية للأطفال الذين تتراوح أعمارهم بين ٦ و٨ سنوات في الكويت

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الخلاصة

الخلفية: تعد سمنة الأطفال في ازدياد في الشرق الأوسط.

الأهداف: هدفت هذه الدراسة إلى تحديد معدل انتشار السمنة بين الأطفال الذين تتراوح أعمارهم بين ٦ و٨ سنوات، واستقصاء إدراك الأمهات عن وزن الأطفال.

طرق البحث: أُجريت دراسة وطنية للبيانات حول الطول والوزن التي تم الحصول عليها من سجلات الممرضات، كما تم تقييم إدراك الأمهات من خلال استبيان ذاتي الإجابة. وتألف حجم العينة من ٢٢٠٨ طفلاً يتوفر لديهم قياسات منسب كتلة الجسم الخاصة بهم، و١٠٠٢ طفلاً يتوفر لديهم قياسات منسب كتلة الجسم الخاصة بهم وإدراك الأمهات.

النتائج: بلغ مجموع معدل انتشار زيادة الوزن والسمنة بين الأطفال ٩ , ٤٠٪ وفقًا للقيم الحدية لمنظمة الصحة العالمية و٧ , ٣٩٪ وفقًا لتصنيفات مراكز مكافحة الأمراض والوقاية منها. كما وجدنا أن إدراك الأمهات عن ٩ , ٧٧٪ من الأطفال المصابين بزيادة الوزن و٤ , ٤٥٪ من الأطفال المصابين بالسمنة أنهم يتمتعون بوزن صحي. إضافة إلى ذلك، ٨ , ٣٩٪ من الأطفال الذين يتمتعون بوزن طبيعي قالت أمهاتهم بأن وزنهم منخفض.

الاستنتاجات: يبعث معدل الانتشار المرتفع المنذر بالخطر للسمنة بين أطفال الكويت، إضافة إلى المدارك المغلوطة لدى الأمهات عن الحالة الفعلية لوزن أطفالهن، على القلق الشديد مما يتطلب تدخلاً عاجلاً في مجال الصحة العامة.

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Availability, pricing and affordability of selected medicines for noncommunicable diseases

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Abstract

Background: The global and national burden of noncommunicable diseases continues to rise, thus making access to medicines increasingly important.

Aims: The objective of this study was to evaluate the availability, pricing, and affordability of selected medicines for noncommunicable diseases in the Islamic Republic of Iran used in 2014 based on the World Health Organization (WHO)/ Health Action International (HAI) methodology.

Methods: The price and availability data for 54 selected medicines were collected from public and private retail pharmacies as well as private pharmacies located in public hospitals in six cities of the Islamic Republic of Iran on the basis of the standardized methodology developed by WHO and HAI. The outcome measures were percentage availability of medicines, ratios of medicine prices to the international reference prices, and the affordability. Affordability was defined as the number of days' wages needed by the lowest-paid unskilled government worker to afford one month of chronic treatment.

Results: The procurement price of the surveyed Lowest Priced Generic and Most Sold Generic medicines was 1.19 times the international reference price. The patient price was not significantly different among different pharmacy retail settings compared with the international reference prices. Moreover, the overall mean availability of the surveyed Lowest Priced Generic medicines in public, private, and other settings was 75.5%, 83.3% and 80.3%, respectively. All the treatment costs for the high burden noncommunicable diseases were less than one day's wages of the lowest-paid government worker.

Conclusions: This study indicated that procurement prices of the surveyed medicines were reasonable in comparison with the international reference price. Moreover, the availability of generic forms of the surveyed medicines was good but originator brand medicines were significantly low in all the three settings.

Keywords: Iran, availability, affordability, health services accessibility, noncommunicable diseases

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Introduction

The burden of noncommunicable diseases (NCDs) is increasing in the low- and middle- income countries. Such diseases are the dominant causes of death, and it is estimated that cancer, cardiovascular, diabetes, and chronic respiratory diseases are the cause of more than 60% of all deaths in 2005 (1), and represent 43% of the burden of diseases and are responsible for the majority of deaths worldwide (2). About 80% of chronic-disease deaths occur in low- and middle-income countries (3). In the Islamic Republic of Iran, the prevalence of NCDs is high (4) and in the past few decades the main cause of mortality in the country has changed from communicable diseases to NCDs (5).

Due to the high prevalence and burden of diseases, Iranian society needs a reliable supply of lifelong and affordable treatments for patients. Since NCDs require life-long treatment, lack of reliable access to and high price of needed medicines are considered as obstacles to adequate treatment. A fundamental step in improving access to medicines for NCDs in the country is measuring the availability and affordability of essential medicines present in different pharmacy settings. To this end, some background knowledge about the Iranian pharmaceutical market is required. In the Islamic Republic of Iran, the government controls pharmaceutical production/importation in order to make it more affordable and in order to keep the costs contained. In addition, nearly all Iranians use some form of insurance system to compensate for their drug expenses (6). The main stakeholder of pharmaceutical affairs is the Iran Food and Drug Administration (IFDA) that seeks to regulate all aspects of pharmaceutical market under the supervision of the Ministry of Health and Medical Education (MoHME) (7). All pharmacies

at all settings provide their medicines from the same officially registered distributors except for vaccines and a few medicines for rare diseases.

The price is set at the level of the lowest priced equivalent on the market (patients must pay extra if requesting a higher priced equivalent product). The patient pays a co-payment and the pharmacy claims back the balance from the insurer (*6*). The premium for insurance coverage is distributed among the employer, the employee, and the government. Both public and private settings are dealt with the same way by the insurance system, which is responsible for reimbursement of medicines. Thus, the whole health system's mission is to provide sufficient, accessible and affordable medications for the whole population (*8*).

A study evaluating the availability and accessibility of primary care medications in the Islamic Republic of Iran was conducted in 2004 and reported very good affordability of drugs and good availability of primary care drugs in public pharmacies (*8*). However, to the best of our knowledge, no study has been carried out so far to evaluate the availability and affordability of particular medicines for NCDs. Therefore, this study investigated the pricing, availability and affordability of selected medicines, used for NCDs in 2014 in order to provide comparable, evidence-based information for policy-makers.

Methods

The methodology for assessing medicine price, availability, and affordability in this study was based on the one developed by the World Health Organization (WHO) and Health Action International (HAI). The survey approach involves the use of a systematic survey to collect data and information on the pricing, availability, and affordability of a core list of medicines in 2014, and provides guidance on reporting and on making policies aimed at resolving the problems. According to this methodology, each country is allowed to select a supplementary list of medicines on the basis of their importance in treating major national health problems (*9*). A validation study of the WHO/HAI survey methodology done in Peru indicated that focusing on commonly used medicines from six regions could yield sufficient and valid results (*10*).

Data collection

The selected medicines were specified as a core list of medicines used in the treatment of NCDs with dosage forms and strengths to be surveyed for each medicine. The medicines included a global core list and a supplementary list. The supplementary list was discussed among experts trying to cover all four groups of NCD medicines including medicines of CVD, diabetes, COPD, and CNS. All the selected medicines were on the Iran National Essential Medicines List during the year 2014. The list was finalized after reaching a unanimous agreement.

The data was collected for 54 medicines from a total of 30 public retail pharmacies, 30 private community retail pharmacies, and 30 private pharmacies located inside public hospital (which are called other settings in this study) in Tehran and five provinces: Khorasan (Mashad), Yazd (Yazd), Sistan va Baluchistan (Zahedan), Gilan (Rasht), and Lorestan (Khoramabad). In the selection of the surveyed cities, the distance to the capital Tehran, population, and diversity in socioeconomical indexes were considered. The lists of health facilities and pharmacies were provided by IFDA regional branches. Data collection was conducted by 18 educated data collectors over two weeks. In addition to all three sectors, the procurement prices were obtained from the three major distributors. For each of the surveyed medicines, the data were collected for originator brand, most sold generic (MSG), and lowest priced generic (LPG) at each facility.

Pricing

The prices and availability of 17 iriginator brands products were recorded: Alprazolam, Amlodipine, Atorvastatin, Carbamazepine, Clopidogrel, Clozapine, Diclofenac, Digoxin, Enoxaparin syringe, Epoetin alpha injection, Hydrocortisone sod succ, Levothyroxine, Metformin, Methylphenidate HCL, Salbutamol inhaler, Sod. Valproate, and Sulphsalazine. However, no originator brand products for the rest of the medicines in the list could be found in the Islamic Republic of Iran. The WHO/HAI survey methodology presents prices in local currency and calculates median price ratios (MPR) in order to facilitate cross-country comparisons. The MPR is computed by dividing the local price by an international reference price in form of local currency.

Medicine Price Ratio (MPR) = median local unit price/international reference unit price. An MPR of 1 means the local price is equivalent to the international reference price, whereas an MPR of 2 means the local price is twice the reference price.

In order to make comparisons feasible, the international reference prices used for this survey were extracted from the 2013 Management Sciences for Health (MSH) International Drug Price Indicator Guide. The MSH Guide collects information from recent price lists of not-profit and for-profit medicine suppliers for multisource medicines and thus reflects the prices governments could be expected to pay at the time of offering for medicines.

Availability

Availability of the medicines was evaluated in all the outlets surveyed and was expressed as the percentage of the outlets in each sector whereby the medicines were available.

Affordability

According to the methodology, routine regimens ("typical" treatments) of a number of NCDs were used to demonstrate the actual affordability for individual patients at a number of settings (*9*). Affordability was calculated as the number of days the lowest-paid unskilled

government worker would have to work to pay for one month's treatment for the medicines for chronic conditions. In the Islamic Republic of Iran, whether in public or private sector, the lowest-paid unskilled government worker is on the minimum salary for all those earning a wage. At the time of the survey, the lowest-paid unskilled government worker earned 270 000 Iranian Rials (IRR) (approximately US$ 8 [2014]) per day. Having to spend more than one day's income per month on family medicine needs is considered to be unaffordable.

Results

Availability

The results from the availability of medicines survey, expressed as originator brand, most sold generic and lowest priced generic were depicted for all the three settings in Table 1. Across the 54 medicines, the mean availability of lowest priced generic in public sector facilities and private pharmacies, and other settings was 75.5%, 83.3%, and 80.3%, respectively. The medicines selected as most sold generic were available in nearly half of public facilities and private pharmacies (Figure 1).

The results from the availability survey indicated that the market was dominated by generics medicines. Of the 54 medicines surveyed, 18 were found in all 30 private pharmacies and only one in public health facilities on the day of data collection. Morphine injections were not found in any of the surveyed private pharmacies and retail pharmacies in public hospitals as they were not permitted. Moreover, of the 54 medicines surveyed, seven were found in all the 30 private retail pharmacies in public hospitals on the day of data collection (Table 2).

Procurement prices

The procurement prices to MPR are shown in Table 3. As it is displayed, in the Islamic Republic of Iran procurement prices were closest to the international reference price for most sold generic and lowest priced generic medicines. The median price for both generic versions was 1.19 times the international reference price; while the overall procurement price for the 11 originator brands found in all the three distributors was 4.02 times the international reference price. As mentioned earlier, public and private procurement systems are the same, and all three selected distributors provide medicines for pharmacies at both settings. Prices of originator brands and generic equivalents are significantly different from those of lowest priced generic and most sold generic.

Table 1: **Availability of survey medicines**

Originator brand	Most sold generic	Lowest priced generic	%
In public health facilities			
Mean availability (%)	25.5	46.4	75.5
SD* availability (%)	27.4	21.0	20.9
In private pharmacies			
Mean availability (%)	39.1	53.3	83.3
SD* availability (%)	33.3	25.9	25.2
In private pharmacies in public hospitals			
Mean availability (%)	24.8	50.6	80.3
SD* availability (%)	26.0	19.8	21.3

** Standard deviation*

Public sector patient prices

The results from the prices in public health facilities showed that in public facilities in the country, patient prices were closest to the international reference price for lowest priced generic medicines (interquartile range 0.6–6.0) (Table 4). From among the 13 originator brands surveyed, nine medicines were found in the public sector facilities and these were four times the international reference price. There was negligible variation in the price of the same medicine in different pharmacies and regions, indicating that the adherence to the regulated prices by IFDA was strict.

Private sector patient prices

In private retail pharmacies, orifinator brand prices were about 3.5 times the international reference price and patient prices for most sold generic medicines were closest to the international reference price (interquartile range 0.15–5.58) (Table 5). As in the public sector, there was negligible variation in prices of the same medicine in private retail pharmacies in different pharmacies and regions.

Other sector patient prices (private pharmacies located in public hospitals)

In the private pharmacies located in public hospitals, originator brands were 3.88 times higher than the international reference price, and lowest priced generics, like most sold generics, were about 1.19 times the international reference prices (Table 6). Similar to the other two settings, there was negligible variation in prices of the same medicine in different pharmacies and regions. Prices in the private pharmacies located in public hospitals were the same as those in private retail pharmacies, reflecting reflect the regulated retail price.

Inter-sectoral comparisons

As shown in Table 7, lowest priced generics had the highest availability at all the three settings and originator brands had the highest availability in private pharmacies. There were not any significant differences the between the settings in the availability of medicine.

Affordability

The affordability of treating seven of the NCDs causing high rates of morbidity and mortality was assessed by comparing the total cost of medicines prescribed at a standard dose. This index was applied to the daily wage of the lowest-paid unskilled government worker (US $8 per day) in Iran at the time of the survey. The result showed that less than one day's wage was needed to purchase all treatments (Table 8). If a typical Iranian worker needed

Table 2: **Availability of survey medicines (n=54 medicines)**

Availability	Medicine
In public health facilities	
Not found	-
< 50%	Carvedilol, Methylphenidate, Levodopa/carbidopa, Tamoxifen, Digoxin, Clozapine, Enoxaparin injection, Fluphenazine injection
50–60%	Lithium, morphine, Epoetin alpha, Gliclazide, Simvastatin, Sulphasalazine
61–80%	Losartan, Folic acid, Chlorpromazine injection, Beclometasone inhaler, Diclofenac, Clopidogrel, Furosemide, Spironolactone, Dimenhydrinate
81–99%	Amlodipine, Atenolol, Glibenclamide, Paracetamol, Valproate, Timolol eye drops, Alprazolam, Amitriptyline, Cetirizine, Epinephrine injection, Hydrocortisone sod succ, Ibuprofen, Isosorbide dinitrate, Levothyroxine, Omeprazole, Atorvastatin, Fluoxetine, Hydrochlorothiazide, Metformin, Phenobarbital, Phenytoin, Trihexylphenidyl, Carbamazepine, Diazepam, Enalapril, Isophane human insulin, Prednisolone, Salbutamol syrup, Neutral sol human insulin, Salbutamol inhaler
100%	Dexamethasone injection
In private retail pharmacies	
Not found	*Morphine injection*
< 50%	Digoxin, Epinephrine injection, Fluphenazine injection
50–60%	Epoetin alpha, Carvedilol, Chlorpromazie
61–80%	Sulphasalazine, Tamoxifen, Clozapine, Hydrocortisone
81–99%	Valproate, Spironolactone, Beclometasone inhaler, Diazepam, Gliclazide, Isophane human insulin, Lithium carbonate, Clopidogrel, Dimenhydrinate, Isosorbide dinitrate, Levothyroxine, Metformin, Neutral sol human insulin, Phenobarbital, Phenytoin, Simvastatin, Trihexylphenidyl, Alprazolam, Amitriptyline, Atorvastatin, Furosemide, Salbutamol inhaler, Salbutamol syrup
100%	Amlodipine, Atenolol, Carbamazepine, Cetirizine, Dexamethasone injection, Diclofenac, Enalapril, Fluoxetine, Folic acid, Glibenclamide, Hydrochlorothiazide, Ibuprofen, Losartan, Omeprazole, Paracetamol, Prednisolone, Timolol maleate eye drops, Acetyl salicyclic acid
In private retail pharmacies located in public hospitals	
Not found	-
< 50%	Carvedilol, Sulphsalazine, Fluphenazine injection, Tamoxifen citrate, Enoxaparin syringe, Methylphenidate HCL
50–60%	Levodopa + carbidopa, Epoetin alpha injection, Morphine injection, Digoxin
61–80%	Dimenhydrinate, Phenobarbital, Lithium carbonate, Sod. Valproate, Phenytoin, Clozapine, Simvastatin, Chlorpromazine injection, Epinephrine injection, Gliclazide, Spironolactone, Acetyl salicyclic acid
81–99%	Amlodipine, Atenolol, Dexamethasone injection, Fluoxetine, Glibenclamide, Isophane human insulin, Isosorbide dinitrate, Levothyroxine, Amitriptyline, Beclometasone inhaler, Carbamazepine, Cetirizine, Enalapril, Folic acid, Furosemide, Losartan, Metformin, Prednisolone, Salbutamol inhaler, Diclofenac, Neutral sol human insulin, Salbutamol syrup, Timolol maleate eye drops, Clopidogrel, Diazepam, Hydrocortisone sod succ
100%	Alprazolam, Atorvastatin, Hydrochlorothiazide, Ibuprofen, Omeprazole, Paracetamol, Trihexylphenidyl

Table 3: **Procurement prices compared to international reference prices (MPR)**

	Most sold generic	Lowest priced generic	%
Number of medications included	11	51	54
Median MPR	4.02	1.19	1.19
25% percentile MPR	2.95	0.65	0.65
75% percentile MPR	16.71	2.21	2.10
Minimum MPR	0.72	0.15	0.15
Maximum MPR	23.53	5.58	5.58

Table 4: **Public sector prices compared to international reference prices (MPR)**

	Originator brand	Most sold generic	Lowest priced generic
Number of medications included	9	52	54
Median MPR	4.02	1.11	1.05
25% percentile MPR	2.38	0.64	0.63
75% percentile MPR	22.36	2.19	1.99
Minimum MPR	1.12	0.15	0.15
Maximum MPR	23.53	5.58	5.58

treatment for hypertension, arthritis, and a peptic ulcer, he had to pay less than half a day's wage every month to purchase the required medicines. The exception was the OB of atorvastatin that required about four days' wages to purchase one month's treatment.

Discussion

The present study is to the best of our knowledge the only one that evaluated the procurement and patient prices and the availability of medicines for NCDs in three different dispensing areas in the Islamic Republic

Table 5: Patient prices in private pharmacies compared to international reference prices (MPR)

	Originator brand	Most sold generic	Lowest priced generic
Number of medications included	14	50	53
Median MPR	3.50	1.18	1.19
25% percentile MPR	1.58	0.66	0.66
75% percentile MPR	10.45	2.23	2.02
Minimum MPR	0.66	0.15	0.15
Maximum MPR	23.53	5.58	5.58

Table 6: Patient prices in private retail pharmacies in public hospitals (MPR)

	Originator brand	Most sold generic	Lowest priced generic
Number of medications included	10	53	54
Median MPR	3.88	1.19	1.19
25% percentile MPR	2.60	0.65	0.65
75% percentile MPR	10.45	2.17	2.01
Minimum MPR	1.12	0.15	0.15
Maximum MPR	23.53	5.58	5.58

Table 7: Availability of the medicines in each sector

	OB	MSG	LPG
Procurement	11	51	54
Public sector	9	52	54
Private sector	14	50	53
Private pharmacies in public hospitals	10	53	54

OB=Originator Brand, MSG= Most Sold Generic, LPG= Lowest Priced Generic

Table 8: Affordability: number of days' wages to purchase treatments

Medicine		Public	Private	Other
Diabetes				
Glibenclamide 5mg (60 tab)	LPG/MSG	0.1	0.1	0.1
Gliclazide 80mg (30 tab)	LPG/MSG	0.2	0.2	0.1
Metformin 500mg (90 tab)	OB	0.6	0.6	0.6
	LPG/MSG	0.2	0.2	0.2
Natural and NPH Insulin 100IU/ml, 3 (10ml vial)	LPG/MSG	1.3	1.3	1.3
Hypertension				
Amlodipine 50mg (30 tab)	LPG/MSG	0.1	0.1	0.1
Atenolol 50mg (30 tab)	LPG/MSG	<0.1	<0.1	<0.1
Hydrochlorothiazide (30 tab)	LPG/MSG	<0.1	<0.1	<0.1
Hyperlipidaemia				
Atorvastatin 20mg (30 tab)	OB	4.1	4.1	4.1
	LPG/MSG	0.2	0.2	0.2
Simvastatin 20mg (30 tab)	LPG/MSG	0.2	0.2	0.2
	26.0	19.8	21.3	
Arthritis				
Diclofenac 50mg (60 tab)	LPG/MSG	0.1	0.1	0.1
Peptic ulcer				
Omeprazole 20mg (30 tab)	LPG/MSG	0.2	0.2	0.2
Asthma				
Beclometasone inhaler	LPG/MSG	0.3	0.3	0.3
Salbutamol inhaler	LPG/MSG	0.3	0.3	0.3
Epilepsy				
Carbamazepine 200mg (150 tab)	OB	-	2.5	2.5
	LPG/MSG	0.5	0.5	0.5

OB=Originator Brand, MSG= Most Sold Generic, LPG= Lowest Priced Generic

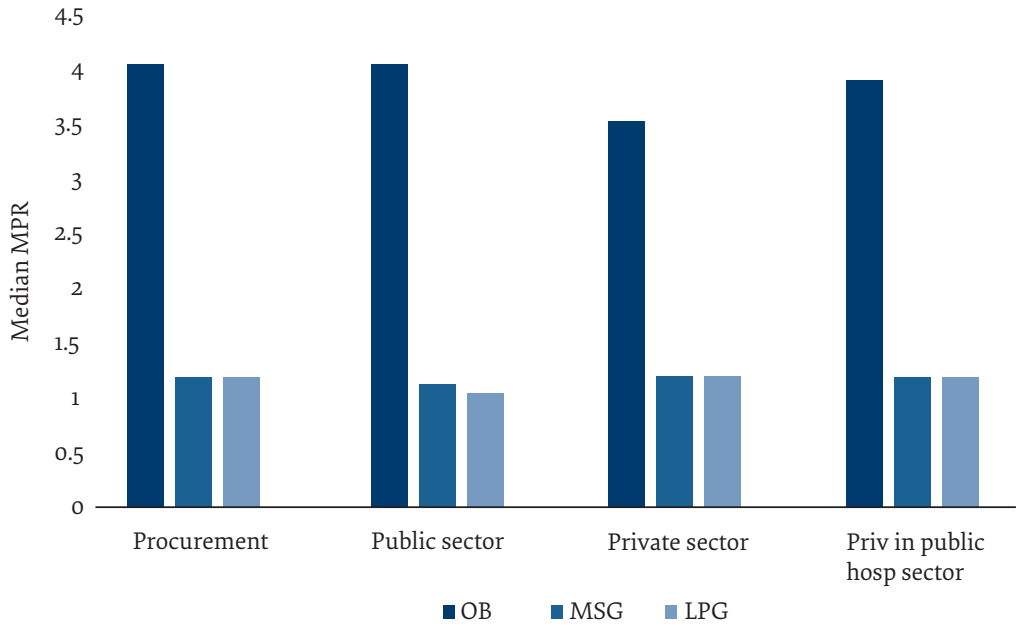
of Iran. The study also assessed the affordability of the treatments according to the WHO/HAI methodology. According to the methodology, the availability less than 30% describes very low, and those of 30–49%, 50–80%, and more than 80% describe low, fairly high, and high availability, respectively (*9*). In order to draw comparisons among countries, the method employs the following cut-off points for MPRs to represent acceptable local price ratios (*8*):

- Public sector – procurement price: MPR ≤ 1
- Public sector – patient price: MPR ≤ 1.5
- Private retail pharmacy – patient price: MPR ≤ 2.5

Hence, in a low or middle-income country like Iran, an MPR of less than or equal to 1 for public sector procurement prices and public sector patient prices indicates acceptable (not excessive) prices (*9*).

The main finding of the study was that the availability and affordability of the selected medicines for NCDs were relatively good for lowest priced generics and most sold generics but not for originator brands. The availability of the generic medicines was relatively good at both public and private settings in the country. The mean availability of lowest priced generic form of the surveyed medicines was fairly high in public pharmacies and high in private pharmacies and other settings. The mean availability of most sold generic ones was low in public pharmacies and fairly high in private pharmacies and other settings. Furthermore, the availability of originator brands medicines seemed to be very low or low in the country, which could be associated with their relatively

Figure 1: Median MPR for medicines with minimum no. of prices



OB=Originator Brand, MSG= Most Sold Generic, LPG= Lowest Priced Generic, Procurement= Procurement prices, Public sector= Public pharmacies, Private sector= Private pharmacies, Priv in public hosp sector= Private pharmacy in public hospital sector

higher prices compared to generics. However, originator brand medicines were more available in the private sector, which could be due to competitive pharmaceutical distributors.

The study also revealed that lowest priced generics were the predominant type of medicine available at all the three settings, which is consistent with other studies using the same methodology (*11*). The Iranian "Generic Scheme" that started in 1980 was successful in improving accessibility to medications, especially during the 1980s (*12*). The national generic medicines policy promotes and enforces the prescribing and dispensing of generic medicines. This finding can be consistent with previous studies (*13*) indicating that the Generic Scheme, started in the 1980s, helped improve accessibility to medicines through decreasing the price of pharmaceuticals and improving national distribution. Nevertheless, some other studies argue that this has also lead to overconsumption, over-use of health care services in the past years, and misuse of some medications (*14*) In the Islamic Republic of Iran, originator brand medicines are more expensive and less available than most sold generics and lowest priced generics; thus, most people have to purchase generic medicines. This finding is also consistent with the previous studies (*15,16*). In the majority of countries, the price of originator brands is higher than those of the two other forms (*17,18*).

The treatments for seven important NCDs cost less than one day's wage for the lowest-paid government worker except for insulin that was costly. Most sold generics or lowest priced generics were reasonably affordable for most conditions while the monthly treatments of two originator brands cost over a day's wage (carbamazepine and atorvastation). It should be noted that the prices did not vary greatly across the three settings.

It is important to note the fact that even in cases where individual treatment seems affordable, some persons or families in need of multiple medications might find it unaffordable (*19*). As outlined by another study (*20*), the WHO/HAI methodology has some limitations despite its strengths. Firstly, availability refers only to the day of the data collection, which might not represent availability over time. Secondly, alternative dosage forms and strengths are not taken into account. Finally, the affordability measure does not include all potential healthcare cost such as diagnostic tests.

This study can have crucial implications for national policy-makers. Some countries such as Lebanon and India (*21*) used the results of medicines price and availability in order to inform the decision and health policy-makers and compose guidelines for improving access to essential medicines. Moreover, using WHO/HAI methodology makes it possible to compare the results with those in other countries in the region or at the same economic level.

Conclusion

In summary, the study set out to explore the availability, pricing, and affordability of essential medicines for NCDs. The data for 54 medicines was collected from public and private sector retail pharmacies and private pharmacies in public hospitals in six Iranian cities on the basis of the standardized methodology developed by the

WHO/HAI. Affordability and mean availability of generic medicines were relatively acceptable across the three settings while OB medicines had lower availability and affordability. The present survey provided a clear picture of the availability, pricing and affordability of essential medicines for NCDs in 2014 in the country. The findings contain important information that policy-makers could use to improve health care policies.

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Disponibilité, prix et accessibilité économique d'une sélection de médicaments pour la prise en charge des maladies non transmissibles

Résumé

Contexte : La charge nationale et mondiale des maladies non transmissibles continue de croître, ce qui donne davantage d'importance à la question de l'accès aux médicaments

Objectifs : La présente étude visait à évaluer la disponibilité et l'accessibilité économique d'une sélection de médicaments pour la prise en charge des maladies non transmissibles et la fixation de leur prix en République islamique d'Iran à l'aide de la méthodologie mise au point par l'Organisation mondiale de la Santé/Health Action International.

Méthode : Les données sur les prix et la disponibilité de 54 médicaments sélectionnés ont été recueillies auprès de pharmacies de détail publiques et privées ainsi que de pharmacies privées situées dans des hôpitaux publics de six villes de la République islamique d'Iran sur la base de la méthodologie normalisée élaborée par l'Organisation mondiale de la Santé (OMS) et Health Action International (HAI). Les résultats ont été mesurés en termes de pourcentage de la disponibilité des médicaments, de ratios des prix des médicaments par rapport aux prix de référence internationaux et d'accessibilité économique. Cette dernière a été définie comme le nombre de jours de salaire nécessaires au fonctionnaire non qualifié le moins bien rémunéré pour se permettre un mois de traitement chronique.

Résultats : Le prix d'achat du médicament générique le moins cher et du médicament générique le plus vendu dans l'étude était 1,19 fois le prix de référence international. Le prix payé par les patients ne variait pas significativement entre les différents établissements de vente au détail en pharmacie par rapport aux prix de référence internationaux. De plus, la disponibilité moyenne globale des médicaments génériques les moins chers inclus dans cette étude dans les établissements publics, privés et autres était de 75,5 %, 83,3 % et 80,3 %, respectivement. Tous les coûts de prise en charge des maladies non transmissibles les plus lourdes étaient inférieurs au salaire journalier du fonctionnaire le moins bien payé.

Conclusions : Cette étude a montré que les prix d'achat des médicaments étudiés étaient raisonnables par rapport au prix de référence internationaux. De plus, la disponibilité des formes génériques des médicaments étudiés était bonne, mais celles des médicaments de marque d'origine étaient très faibles dans les trois types d'établissements.

مدى توافر أدوية محددة لعلاج الأمراض غير السارية وأسعارها والقدرة على تحمل تكاليفها

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الخلاصة

الخلفية: لا يزال العبء العالمي والوطني للأمراض غير السارية في ازدياد، ما يزيد من أهمية الحصول على الأدوية.

الأهداف: كان الغرض من هذه الدراسة هو تقييم مدى توافر أدوية محددة لعلاج الأمراض غير السارية وأسعارها والقدرة على تحمل تكاليفها في جمهورية إيران الإسلامية، والتي تم استخدامها في عام ٢٠١٤، استنادًا إلى منهجية الهيئة الدولية للعمل في مجال الصحة.

طرق البحث: تم جمع بيانات الأسعار والتوافر الخاصة بأربعة وخمسين دواءً محددًا من صيدليات البيع بالتجزئة في القطاعين العام والخاص بالإضافة إلى الصيدليات الخاصة الموجودة داخل المستشفيات العامة في ست مدن بجمهورية إيران الإسلامية، استنادًا إلى المنهجية القياسية التي وضعتها منظمة الصحة العالمية والهيئة الدولية للعمل في مجال الصحة. وشملت مقاييس النتائج النسبة المئوية لتوافر الأدوية، وأسعار الأدوية نسبة إلى الأسعار المرجعية الدولية، والقدرة على تحمل التكاليف. وتم تعريف القدرة على تحمل التكاليف على أنه أجور عدد أيام العمل المطلوبة من العامل غير الماهر الأدنى أجرًا لتحمل تكاليف شهر واحد من علاج الأمراض المزمنة.

النتائج: بلغ سعر شراء الأدوية الجنيسة الأدنى سعرًا والأدوية الجنيسة الأكثر مبيعًا المشمولة في الدراسة الاستقصائية ١٩ , ١ ضعف السعر المرجعي الدولي. ولم يكن سعر البيع للمرضى مختلفًا كثيرًا بين صيدليات البيع بالتجزئة المختلفة مقارنة بالأسعار المرجعية الدولية. إضافة إلى ذلك، بلغ متوسط معدل إجمالي توافر الأدوية الجنيسة الأدنى سعرًا المشمولة في الدراسة الاستقصائية في الصيدليات العامة والخاصة والأخرى ٥ , ٧٥٪، و٣ , ٨٣٪ و٣ , ٨٠٪، على التوالي. وبلغت تكاليف علاج العبء المرتفع للأمراض غير السارية أقل من أجر يوم عمل واحد للعامل الأدنى أجرًا في القطاع الحكومي.

الاستنتاجات: أشارت هذه الدراسة إلى أن أسعار شراء الأدوية المشمولة في الدراسة الاستقصائية تعد معقولة مقارنة بالسعر المرجعي الدولي. بالإضافة إلى ذلك، كان توافر الأنواع الجنيسة من الأدوية المشمولة في الدراسة الاستقصائية جيدًا، ولكن توافر أدوية العلامة التجارية الأصلية كان متدنيًا إلى حد كبير في جميع الصيدليات العامة والخاصة والأخرى.

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Management of patients with metastatic colorectal cancer in Lebanese hospitals and associated direct cost: a multicentre cohort study

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Abstract

Background: For metastatic colorectal cancer a series of novel therapies has emerged during the last decade but their use in routine clinical practice and their costs are not well documented.

Aims: This study evaluated the clinical effectiveness of metastatic colorectal cancer patients in Lebanese oncologic units and estimated the costs.

Methods: A prospective cohort study was conducted on metastatic colorectal cancer patients during 2008–2013. The type of medical management, overall survival and total costs from diagnosis to death were described. Cost analysis was performed using tariffs from 2013 in US dollars.

Results: One hundred and seventy-nine metastatic patients were selected among which 84.9% had colorectal cancer involvement. The average follow-up from diagnosis until death or the latest news was 34.8 months. Around 49.7% were still alive at last follow-up date. Three lines of treatment accounted for 4.5%, 39.6% and 55.9% with an average duration of 14.5, 11.4 and 14.6 months respectively. A 73.2% of patients benefited from targeted therapy. The median overall survival was 20.8 months. The mean total costs of drugs was $22 256 in patients with standard therapy alone whereas the cost increased to $80 396 after the addition of targeted therapy. The mean global total cost was estimated at $64 805 per patient (min $3703; max $304 086).

Conclusions: Targeted therapy associated to standard therapy is highly prevalent in Lebanon in metastatic disease and the associated medical cost substantial. This study is the first to show the clinical effectiveness and costs of targeted therapy in patients with metastatic colorectal cancer.

Keywords: metastatic colorectal cancer, cytotoxic agents, targeted therapies, effectiveness, cost.

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Introduction

Colorectal Cancer is the second most commonly reported cancer in females and the fourth most commonly reported cancer in males in Lebanon, averaging 630 cases in 2012 (*1*). There are no vital statistics or information on the burden of the disease in terms of morbidity or mortality, but its incidence rate in 2015 per 100 000 population, by colon and rectum sites, was 17.6% and 7.5% respectively (*2*). In the Lebanese medical system, analysis of colorectal cancer is not robust and there has been a noticeable increase in risk factors such as poor diet, physical inactivity, obesity, cigarette smoking, heavy alcohol consumption, familial history and genetics. Moreover, the health financing methods are complex and vary according to socio-professional demographics (*3,4*).

Despite these problems mortality rates have declined since the 1980s. Clinical evidence suggests that advances in technology, increase in number of colonoscopy examinations, more opportunistic screening, earlier diagnosis and improved surgery, development of adjuvant chemotherapy and palliative care (*5*), confer survival benefits as well as better symptom control and palliation. Cytotoxic agents are well established as clinically effective and cost-effective treatment options for metastatic colorectal cancer. Clinical research has focused on monoclonal antibodies that selectively target receptors involved in cancer progression with many studies evaluating their efficacy (*6–10*).

As new treatments become available (*11*), there's a need to consider not only their effectiveness in clinical practice, but also their associated costs in comparison to current standard therapies. The way such novel therapies are used and positioned in daily routine practice (as well as their related effectiveness and costs) are not well documented in Lebanon. The aim of this study is to evaluate the management of patients with metastatic colorectal cancer in two Lebanese hospitals, in particular

the comparative effectiveness of cytotoxic agents and targeted therapy along with their estimated direct cost.

Methods

Study design and participants

A prospective study was conducted on a cohort of patients diagnosed with metastatic colorectal cancer in two Lebanese oncology departments (CHU Centre Hospitalier Notre Dame de Secours, Byblos, and CHU Hotel Dieu de France, Beirut) between 1 January 2008 and 31 December 2013. Patients were classified as those treated by cytotoxic agents alone during the whole follow-up period and those treated at any time during their follow-up by chemotherapy plus monoclonal antibodies, depending on disease progression. Eligible participants were all patients with a histologically confirmed adenocarcinoma of the colorectum, with one or more metastases and no previous chemotherapy for metastatic disease. The ethic committees of the two participating centers waived the need for approval since the study was retrospective, anonymous and respected the individuals' confidentiality.

Clinical data

For each patient, data were collected for sex, age at diagnosis, date of the beginning of metastatic disease, type of cancer, histological type, KRAS (Kirsten Rat sarcoma viral oncogene) status, tumor markers, number and type of metastases, and whether it was first, second or third relapse. Patterns of care were described, type of medical management at diagnosis and after recurrence. The type of chemotherapy, RECIST (Response Evaluation Criteria In Solid Tumors) criteria, toxicities, the date of the latest news and/or death, as well as the number of lines and cycles of chemotherapy given were also reported.

KRAS assessments

The mutation status of the KRAS gene is linked to increased tumor aggressiveness, resistance to therapy and poor survival rate *(12)*. Detection of KRAS status has become part of the standard work-up of patients with metastatic colorectal cancer, and tumors that harbor the mutation have been shown to be nonresponsive to anti-EGFR (Epidermal Growth Factor Receptor) therapies (Cetuximab) (*4*, *13–16*). This test is performed in the Pathology National Institute, Beirut, Lebanon, in formalin-fixed, paraffin-embedded tissue collected from patients for whom the resected primary tumor was available and is free-of-charge, likewise the RAS test, but the BRAF test is expensive (these two tests have been performed in Lebanon since 2014).

Lines of therapy

Most patients with advanced colorectal cancer can receive multiple treatment regimens, with therapies changed when needed in order to optimize response or as a consequence of toxicity, patient preference, or disease progression. New options are chosen in a way that is complementary to the previous regimen. In order to prevent confusion, first-line therapy was defined as all chemotherapy and/or biological drugs given to a patient during the first 36 days after initiation of treatment and administered for one or more cycles. Discontinuation of a single drug from a combination regimen was not considered a change in line therapy. The addition of a new regimen or substitution of cytotoxic or a biological agent (for progression or relapse) was considered a new line of therapy.

Costs

Estimating the cost of colorectal cancer treatments in Lebanon is very difficult, mainly due to differences in coverage systems (Ministry of Health, National Social Security Funds, Lebanese Army, private patients, insurances etc.), and changes in prices between 2008 and 2013. Cost analysis was performed under the Lebanese Sickness Fund perspective using tariffs from 2013 in US dollars without any discount rate applied and included:

- Direct costs, as defined as chemotherapy medications (and biotherapy), costs per treatment cycle and total costs per patient. We did not include the cost of administration, supportive medications, physician consultations or treatment of complications. Chemotherapy treatment doses were given proportionally to body surface area.
- Indirect costs (transportation costs, surgery, imaging tests) have not been taken into account due to difficulties in accessing administrative medical records.

We assessed the episodes of care costs in the period considered (protocols and lines during hospitalizations and at home). The unit costs from 2013 were obtained from the cost accounting system of the two hospitals regardless of the coverage system of each patient. Cost values in this year were considered to be representative of the study period. Assigning the same year-specific cost unit to each healthcare service, any differences in cost over time would reflect changes in resource utilization and not in price deviations arising from pharmaceutical companies' policies or different production structures over the study period. Taking into account the date of each care episode and service, monthly costs were assessed (cost histories), and the year of diagnosis was considered the baseline year (Year Zero).

Long-term or lifetime costs are defined as the cumulative cost from the date of diagnosis to the date of death, but in long-term cost estimations some patients are not actually followed until their death, therefore these cost histories are censored (*13,17–19*). However, this introduces a problem; total cost is underestimated when based on the full sample of censored and non-censored cases, since patients who withdraw from the study, or who remain alive at the end of the follow-up period, will continue to incur costs after the study is over. On the other hand, if long-term cost is only estimated for patients with uncensored costs, the estimator is biased towards patients with shorter survival times because

longer survival times are more likely to be censored. Therefore, censored data can lead to biased estimates if the appropriate analysis techniques are not used.

Effectiveness was evaluated by overall survival corresponding to the mean time from diagnosis to death (or date of last follow-up at time of data collection). Primary endpoints were overall survival, progression free survival (PFS), RECIST, progression of the disease (PD) or tumour response rate (TRR), response rate (RR), disease control rate (DCR) and costs.

Tumour assessments

Therapy response in solid tumours was assessed by measuring change in tumour size. RECIST is a standard measurement method that evaluates response to therapy by computed tomographic scans (CT) (*13,17–18,20*). However CT scans do not permit characterization of tumour heterogeneity and its change over time. CT measurements are dependent on the expertise of the observer and discrepancies among observers have been described to be as high as 15 to 40% (*19–20*). Baseline tumour response was assessed every two cycles (6 weeks) according to RECIST version 1.1 (*21-22*) and all patients were monitored every three months for a minimum of two years.

Definition of endpoints

In this study, the following definitions were used to assess therapeutic effectiveness: PFS is defined as the time from randomization until objective tumour progression or death from any cause, and censoring patients who are lost to follow-up; PFS1 is the period from the first enrollment to the confirmation of PD , death or last follow up, whichever occurred first; PFS2 is the period from the first PD, where mostly biological agents were started, to the confirmation of secondary PD or death; PFS3 is the period from the second confirmation of PD to the third PD or death, where a third line (or salvage) therapy was used; time to tumor progression (TTP) is the period from the date of enrollment until the date of discontinuation of treatment or the date of PD confirmation (it does not count patients who die from other causes); overall response rate (ORR) is the sum of partial responses plus complete responses and is a direct measure of drug antitumor activity (direct therapeutic effect); and disease control rate (or rate of non-progression) is classified as complete response, partial response, or stable disease.

Statistical analysis

Categorical variables were presented as counts and percentages and compared using Pearson's chi-squared test or Fisher's exact test, as appropriate. Quantitative variables were presented as mean ± standard deviation and compared using Student's *t*-test. Time since diagnosis was used as time variable. We compared patients' characteristics between groups, progression according to lines used and their relative costs.

In order to compare the effect of therapies (cytotoxic vs target + cytotoxic) on survival, a Cox proportional hazards regression was conducted to assess independent predictors of time to death after colorectal cancer. Patients were reported alive or dead at the end of their follow-up time. Variables associated to the time to death in the bivariate analysis ($P < 0.2$), were included in the multivariate model. Hazard ratios (HR) with 95% confidence intervals (CI) were reported.

Each variable was used as a time-dependent covariate in a cox bivariate regression to evaluate the proportional hazards assumption, which was subsequently confirmed and we compared the overall effect of both groups on survival. We subsequently conducted a sensitivity analysis between every line of treatment and its association with survival. Survival curves were then plotted to show differences in survival for each type of treatment. In addition, the response scores (RECIST) were divided into dichotomous variables (progression vs non-progression, partial or complete response) to study the effect of treatment (cytotoxic vs target) on disease progression (RECIST 1, 2 and 3). For this purpose, a logistic regression was conducted for each RECIST, taking into consideration variables found to be associated with the dependent variable in the bivariate analysis ($P < 0.2$). Analyses were performed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA) and a *P*-value less than 0.05 was deemed statistically significant.

Results

Study process and termination

A total of 179 patients were enrolled between January 2008 and December 2013. Mean age at diagnosis was 60.5 (± 13.2) years and 57.5% were males. The final follow-up of the study was on 30 December 2014 (the median follow up time was 31 months). The details of the baseline patient demographics and clinical characteristics are shown in Table 1.

Treatments

Among the 179 patients diagnosed with metastatic colorectal cancer, as first-line treatment 48 patients were provided chemotherapy alone while 131 patients received chemotherapy plus targeted therapy. After disease progression, and regardless of what regimen was used, 171 (95.5%) went on to receive second-line treatment and 99 (55.3%) received third-line treatment. Table 2 shows that targeted therapy was mostly added to treat aggressive disease (14 vs 86%, 58 vs 42%, 89 vs 11%; $P < 0.001$) in association to cytotoxic conventional treatment.

Bevacizumab was mostly added to fluorouracil-based regimens in the first-line setting and beyond progression (13.0%, 47.3% and 84.4%; line 1 to 3 respectively) whereas Cetuximab was only restricted to patients whose KRAS status was performed and showed a non-mutant gene (1.1%, 9.4% and 15.6%; line 1 to 3 respectively) (Table 2).

Clinical effectiveness and survival

Adding targeted therapy to conventional treatment did not improve the response rate in patients presenting pro-

Table 1: General baseline characteristics of the 179 patients

Characteristics	Total (%)	Cytotoxic group (N/%)	Cytotoxic + targeted group (N/%)	*P*-value
Arms of treatment	179	48 (26.8%)	131 (73.2%)	-
Age at diagnosis, years Range	26-89y	27-83y	26-89y	
Mean[1]	60.5y ± 13.2	63y ± 14.1	59.5y ± 12.9	0.130
Sex				
Males/females	103 (57.5%)/76 (42.5%)	28 (58%)/20 (42%)	75 (57%)/56 (43%)	0.947
Location of primary tumour				
Colorectal	152 (84.9%)	38 (79%)	114 (87%)	0.470
Rectal	60.5y ± 13.2	63y ± 14.1	59.5y ± 12.9	
Location of metastases				
Liver only	50 (28%)	21 (44%)	29 (22%)	
Liver and others	76 (43%)	8 (17%)	68 (52%)	0.002
Non liver	53 (29%)	19 (39%)	34 (26%)	
Number of metastatic sites				
1	92 (52%)	40 (85%)	52 (40%)	0.044
≥2	86 (48%)	7 (15%)	79 (60%)	
KRAS gene status				
Wild	93 (52%)	11 (23%)	82 (63%)	
Mutated	27 (15.1%)	2 (4%)	25 (19%)	0.001
ND*	59 (33%)	35 (73%)	24 (18%)	
Tumour markers				
CEA only	55 (31%)	10 (21%)	45 (34%)	
CA19.9 only	11 (6%)	3 (6%)	8 (6%)	
Both increased	50 (28%)	7 (15%)	43 (33%)	0.001
Neither increased	63 (35%)	28 (58%)	35 (27%)	
Duration of treatment or follow up (in months) (All lines combined)	Median: 30.9 months Mean: 34.7 months ± 19.2 Min: 3.0 months Max: 71.5 months	Median: 36.5 months Mean: 36.1 months ± 21.2 Min: 3.0 months Max: 71.5 months	Median: 30.4 months Mean: 34.2 months ± 18.5 Min: 3.5 months Max: 69.0 months	0.473

**Lack of appropriate consent or lack of samples, [1]Data are in % or median (± standard deviation), CEA: CarcinoEmbryonic Antigen, CA19.9: Cancer antigen.*

Table 2: Percentage of cytotoxic and targeted chemotherapy agents applied in the 3 lines of treatment (after relapse) and number of cycles received

Treatment	1st line	2nd line	3rd line	*P*-value
Conventional (chemotherapy)	154 (86%)	72 (42%)	26-89y	<0.001
Targeted	25 (14%)	99 (58%)	59.5y ± 12.9	
Treatment strategies targeted (associated to chemotherapy):				
Cetuximab	1.1%	9.4%	15.6%	NS
Bevacizumab	13.0%	47.3%	84.4%	
Conventional chemotherapy:				
5FULV	36.3%	0.6%	8.3%	
XELOX	25.7%	37.4%	24.0%	
FOLFOX	38.6%	43.3%	47.0%	NS
FOLFIRI	1.1%	12.9%	5.2%	
FOLFOXIRI	-	16.4%	1.1%	
XELIRI	-	4.7%	34.4%	

Table 2: Percentage of cytotoxic and targeted chemotherapy agents applied in the 3 lines of treatment (after relapse) and number of cycles received (*concluded*)

Treatment	1st line	2nd line	3rd line	*P*-value
Cycles				
≤ 4 cycles	16.8%	15.6%	56.4%	NS
5 - 6 cycles	41.9%	27.4%	-	
7 -8 cycles	19.0%	30.7%	-	
≥ 9 cycles	22.3%	21.8%	-	

5FU/LV = Fluorouracil/Leucovorin, FOLFOX = Fluorouracil, Leucovorin, and Oxaliplatin; XELOX = Capecitabine and Oxaliplatin; FOLFIRI = Irinotecan, Fluorouracil, and Leucovorin, FOLFOXIRI = Fluorouracil, Leucovorin, Oxaliplatin and Irinotecan, XELIRI = Capecitabine and Irinotecan. NS = Non-significant.

gression of the disease (Table 3), with 17% in the cytotoxic group vs 16% in the targeted + cytotoxic group ($P > 0.05$); 57 vs 11% ($P < 0.05$) and 18 vs 14% ($P > 0.05$) from line 1 to 3 respectively; whereas the disease control rate was improved in the third line therapy (61% in the cytotoxic group vs 56% in the targeted + cytotoxic group, but the difference was not statistically significant). In addition, the PD (or TTP) was higher in cytotoxic + targeted group in lines 1 and 2 (40 vs 44% and 29 vs 46%), but decreased in line 3 (82 vs 67%); however, the difference was not statistically significant with a higher cost (min. = $127 184; max. = $304 086)

The median PFS was 35 months in the first line cytotoxic group and 31 months in the cytotoxic + targeted group, ($P = 0.01$) whereas in the second and third line, it was 37 months vs 34.8 months ($P = 0.99$) and 27 months vs 34.2 months ($P = 0.37$) respectively (Table 3). KRAS gene status was evaluated in 120 tumors; 58 samples were excluded because of lack of samples or inappropriate consent. An activating KRAS mutation was found in 27 tumors (15.1%), nine patients (33.3%) with KRAS mutation were still alive whereas in wild KRAS patients (n = 93, 52%), 39 (41.9%) stayed alive ($P = 0.001$). The response rate was significantly lower in those with KRAS mutations than in those with wild-type KRAS tumors (6% vs 28%, $P = 0.01$)

The number of metastases at the time of diagnoses and recurrence greatly influenced the response to treatment and consequently the rate of survival. Eighty-six (48%) patients had ≥ 2 metastases, of whom 32 (37.2%) responded to treatment, whereas for patients having only one metastatic site (n = 92, 52%), the response to treatment was 54.3%.($P = 0.044$). Overall response rate was inferior in patients having ≥ 2 metastases than in patients with only one metastasis (18% vs 47%, $P = 0.004$).

Survival results

The Kaplan-Meier survival curve of the metastatic colorectal cancer cohort is displayed in Figure 1. The median of survival in the whole population was 20.8 months (625 days) (CI 95% = 10.7–30.9 months); 49.7% were still alive at the end of the study. Survival analysis revealed that the addition of targeted therapy failed to improve mCRC patients' survival ($P < 0.002$).

Adjusted survival analysis

In the multivariate model adjusted for age, number of metastases and toxicities, only toxicities were found

Table 3: Tumour assessment responses and effectiveness of treatment, all protocols combined

Outcomes	1st line		*P	2nd line		*P	3rd line		*P
	Cytotoxic (N=153)	Targeted + cytotoxic (N=25)		Cytotoxic. (N=71)	Targeted + cytotoxic (N=99)		Cytotoxic (N=11)	Targeted+ cytotoxic (N=88)	
Tumour response rate									
Complete response	6(4%)	1(4%)		18(25%)	7(7%)		1(9%)	6(7%)	
Partial response	20(13%)	3(12%)		12(17%)	4(4%)		1(9%)	6(7%)	
Stability	67(44%)	10(40%)		21(29%)	42(43%)		0(0%)	17(19%)	
Progression	60(40%)	11(44%)	20.975	21(29%)	46(46%)	0.000	9(82%)	59(67%)	0.5
Disease control rate (%)	61	56		71	54		18	33	
Response rate (%)	17	16		57	11		18	14	
Progression of the disease (%)	40	44		29	46		82	67	
Progression free survival (months)**	35	31	0.01	37	34.8	0.99	27	34.2	0.37

**NS = non-significant*

*** Progression free survival or length of treatment or duration of each line PFS1; PFS2 &PFS3 are the 3 lines or periods free of the disease in the life of the patient*

Table 4: Cox survival analysis of factors associated to time to death (bivariate and multivariate results)

Variable (N patients)	Unadjusted				Adjusted**			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Arm A (48) vs Arm B* (131)	0.50	0.29	0.87	0.014	0.76	0.41	1.40	0.379
Age at diagnosis	1.0	0.98	1.01	0.852	1.00	0.99	1.02	0.785
Males (103) vs Females (75)	1.49	0.96	2.31	0.075	-	-	-	-
Markers (reference) Not ↑ (63)								
CEA↑(54)	1.77	1.00	3.15	0.052	-	-	-	-
Ca19.9↑(11)	1.71	0.69	4.23	0.243	-	-	-	-
Both↑(50)	2.95	1.72	5.04	0.000	-	-	-	-
Toxicities (reference) Grade 2 (24)								
Grade 3 (110)	12.79	1.77	92.68	0.012	11.50	1.58	83.79	0.016
Grade 4 (44)	33.16	4.55	241.66	0.001	28.71	3.91	210.60	0.001
≥ 2 metastases (86) vs 1 metastases (92)	1.86	1.21	2.85	0.004	1.46	0.91	2.34	0.117
Liver metastases (45) vs No liver metastases (133)	0.57	0.33	0.98	0.041	-	-	-	-

Arm A cytotoxic agents; Arm B cytotoxic agents and targeted therapy.

***Multivariate cox regression with a forward stepwise entry.*

Table 5: Independent predictors of progression (RECIST 1) after the first-line of treatment (N=178)

Variable	Categories	Adjusted OR	95% CI	*P*-value*
First-line treatment	Cytotoxic vs targeted +cytotoxic	1.13	0.46-2.78	0.790
Number of metastases	≥ 2 vs 1	1.87	0.94-3.72	0.074
Toxicities	Grade 2 (reference)			
	Grade 3	2.81	0.87-9.12	0.085
	Grade 4	4.48	1.26-15.92	0.021
Markers	No ↑ (reference)			
	CEA↑	2.46	1.08-5.60	0.033
	Ca19.9↑	1.89	0.48-7.36	0.362
	Both↑	1.67	0.69-4.07	0.256

Multiple logistic regression (variables associated to progression with a P-value < 0.2 in the bivariate analysis were entered in the model).

Table 6: Independent predictors of progression (RECIST 2) after the second-line of treatment (N=170)

Variable	Categories	Adjusted OR	95% CI	*P*-value*
Second-line treatment	Cytotoxic vs targeted +cytotoxic	0.55	0.26-1.17	0.120
Number of metastases	≥ 2 vs 1	2.21	1.03-4.74	0.041
Toxicities	Grade 2 (reference)			
	Grade 3	3.43	0.70-16.70	0.128
	Grade 4	10.14	1.92-53.46	0.006
Markers	No ↑ (reference)			
	CEA↑	1.40	0.55-3.60	0.480
	Ca19.9↑	6.81	1.52-30.57	0.012
	Both↑	3.35	1.27-8.84	0.014

Multiple logistic regression (variables associated to progression with a P-value < 0.2 in the bivariate analysis were entered in the model).

Table 7: Independent predictors of progression (RECIST 3) after the third-line of treatment (N=99)

Variable	Categories	Adjusted OR	95% CI	*P*-value*
Third-line treatment	Cytotoxic vs targeted +cytotoxic	4.02	0.45-36.11	0.214
Number of metastases	≥ 2 vs 1	1.09	0.32-1.74	0.895
Toxicities	Grade 2 (reference)			
	Grade 3	-	-	-
	Grade 4	-	-	-
Markers	No ↑ (reference)			
	CEA↑	0.39	0.09-1.74	0.217
	CA19.9↑	1.91	0.15-24.96	0.621
	Both↑	1.01	0.19-5.30	0.991

**Multiple logistic regression (variables associated to progression with a P-value < 0.2 in the bivariate analysis were entered in the model).*

Table 8: Average overall total cost ($) /arms of treatment

	1st line	2nd line	3rd line		*P*-value
Cytotoxic group ($)					
Mean ± SD	7961 ± 7469	15 149 ± 10 873	4958 ± 5388	22 255 ± 10 525	<0.05
Minimum	367	1139	649	3703	
Maximum	40 089	38 292	12 764	44 121	
Median	7692	11 454	2044	20 490	
Targeted + Cytotoxic group ($)					
Mean ± SD	15 302 ± 21 974	46 947 ± 38 312	28 290 ± 18 451	80 395 ± 49 047	<0.05
Minimum	183.6	1800	1909	7197.8	
Maximum	127 184	243 394	77 775	304 086	
Median	7692	40 537.2	24 516.8	73 424.24	
Global Cost ($)					
Mean ± SD	13 333 ± 19 443	38 951 ± 36 294	26 589 ± 18 825	64 805 ± 49 530	<0.05
Minimum	183	1139	649	3703	
Maximum	127 184	243 394	77 775	304 086	
Median	7692	31 910	24 456	57 743	

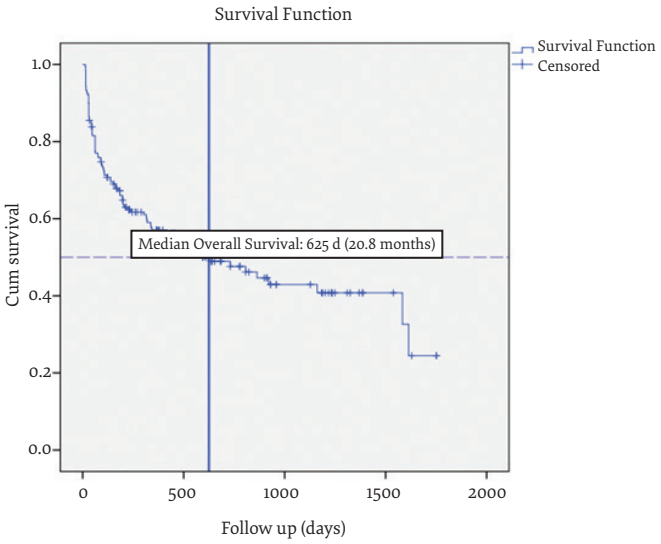
Table 9a: Cost for every single treatment (Tariffs 2013)

Drug	Administration	Price/injection	Cost/dose	Cost/cycle (2 weeks)
Bevacizumab	5 mg/kg/d/2 weeks	100 mg = $718 400 mg = $2 443	$2443	$7329
Cetuximab	400 mg/m2 (Loading dose) 250 mg/ m2 (Maintenance dose)	5mg/ml (20 ml) = $351 5mg/ml (100ml) = $1467	$2520	$3573

Table 9b: Cost for every single treatment (Tariffs 2013)

XELOX (Cycle of 21d)	FOLFOX-6 (Cycle of 14d)	FOLFOX-4 (Cycle of 14d)	FOLFIRI (Cycle of 14d)
Oxaliplatin $1 481 Capecitabine $428	Oxaliplatin $1 139 Leucovorin $76 5-FU (Bolus) $2.50 5-FU (Perfusion) $14.90	Oxaliplatin $969 Leucovorin $76 5-FU (Bolus) $2.50 5-FU (Perfusion) $3.71	Irinotecan $518 Leucovorin $76 5-FU (Bolus) $2.50 5-FU (Perfusion) $3.71
Total = $1909	**Total = $1233**	**Total = $1051**	**Total = $600**

Figure 1: Kaplan–Meier curve for OS in the study cohort (N = 179) of mCRC patients



to be an independent predictor of the time to death (Table 4) (grade 3 vs grade 2; HR=11.50. 95% CI=[1.578-83.79]; *P* = 0.016; grade 4 vs grade 2; HR=28.71; 95% CI=[3.91-210.59]; *P* = 0.001). No difference was observed when comparing cytotoxic group patients (Group A) to cytotoxic-targeted group patients (Group B) (*P* = 0.379). In the sensitivity analysis between the three lines of treatment, a slightly positive result was observed for Group B vs Group A for time to death in lines two and three, but the difference was not statistically significant. Thus, survival analysis revealed that the addition of targeted therapy failed to improve mCRC patients' survival (Figure 2).

Treatment and RECIST

In the multivariate models adjusted for the number of metastases (≥ 2 metastases vs 1 metastasis), toxicities (grades 2 and 4) and markers (increase in CEA and/or CA19.9), the association between treatment (cytotoxic or cytotoxic+targeted) and RECIST (progression vs no progression) was not statistically significant in all three lines of therapy (Table 5, Table 6, Table 7). We did not include "KRAS mutations" in the multivariate models because of the high number of missing values (58 missing).

Colorectal cancer treatment costs

The corresponding costs of cytotoxic and targeted drugs are shown in Table 8, Table 9a and Table 9b. The corres-

Figure 2: Cox Survival curves showing the differences on survival between the 2 groups and the 3 lines of therapy respectively (after adjustment for age, number of metastases and toxicities). In the sensitivity analysis between the 3 lines of treatment, a slight advantage of the cytotoxic + targeted group versus cytotoxic on time to death was shown in lines 2 and 3 although not statistically significant.

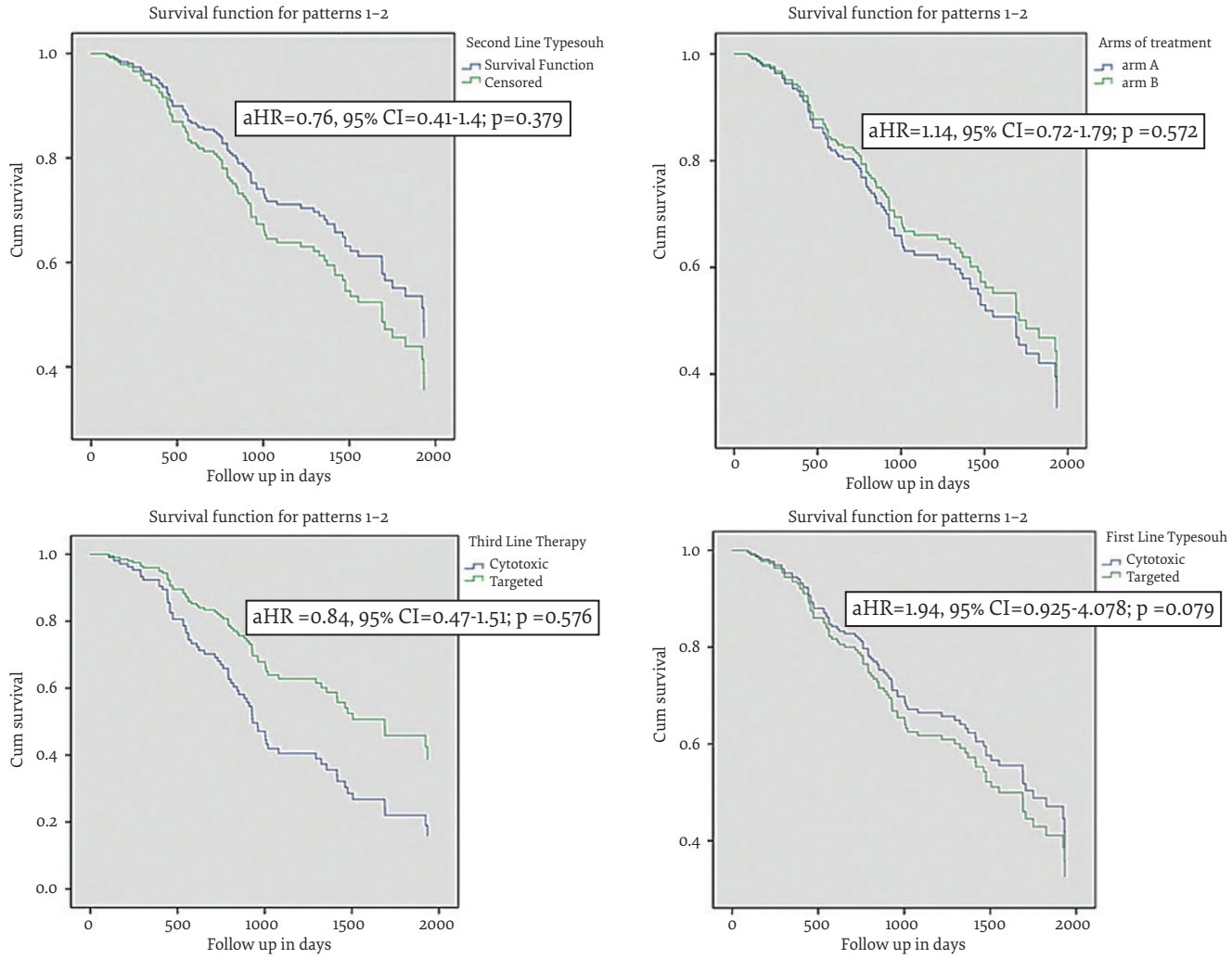
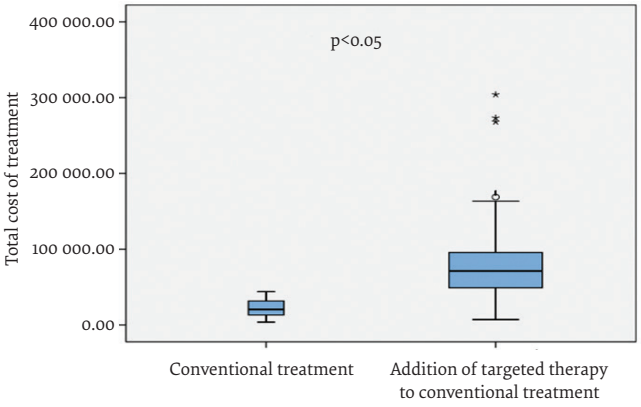


Figure 3: "Box-Plot" diagram of the total global costs in patients with mCRC in our study



ponding total costs for all lines combined are as follows: cytotoxic group = $22 255 ($P < 0.05$), cytotoxic associated to targeted therapy = $80 395 ($P = 0.001$) and global total cost = $64 805 ($P = 0.000$), respectively (min. = $127 184; max. = $304 086). As shown in the Box-Plot diagram (Figure 3), the addition of targeted therapy to conventional treatment demonstrates an approximate fourfold increase in expense.

Discussion

According to the current available literature, this is the first study to estimate the real costs (cost of the disease) of chemotherapy associated to biotherapy for metastatic colorectal cancerfrom the perspective of the Lebanese public health system, using accurate cost-related data. Few studies have evaluated general costs of specific treatments for cancer in high-income countries (*19,23–25*). Most studies on treatment costs of metastatic colorectal cancer compared the costs of XELOX with FOLFOX-6 regimens, since it is suggested that both therapies are similar in terms of efficacy and safety. A cost-minimization study conducted in Australia has demonstrated that the use of XELOX in first-line and second-line treatment for metastatic colorectal cancer reduced the average cost by $9110 and $7113 respectively, as compared with mFOLFOX (*26*). From the French health insurance perspective, when compared with mFOLFOX-6, XELOX resulted in lower costs related to drug acquisition and shorter hospitalizations per patient (*23,24*).

With the exception of 5-FU and irinotecan, these drugs are very expensive and the cost implications of these promising medications are the subject of significant debate (*8–10,26–28*). There are limited data in the published literature regarding the cost effectiveness of treatments for patients with metastatic colorectal cancer. Hillner used data from the multicenter study NCCTG 9741 to compare treatment with FOLFIRI to FOLFOX and found that the 4.4 month median survival benefit of the FOLFOX arm was accompanied by an incremental cost of $29 953, resulting in an incremental cost effectiveness ratio (ICER) of $80 410 per life year gained (*11,29*). Starling examined the role of cetuximab and irinotecan compared to best supportive care from the perspective of the United Kingdom National Health Service and found an ICER of GBP£42 975 per life year gained (*17,21*). To our knowledge, there has not been a comprehensive cost effectiveness analysis that includes multiple lines of therapy.

Despite recent advances in early detection and therapeutic intervention, colorectal cancer remains one of the most deadly cancers in Lebanon. While surgical removal leads to high cure rates of localized disease, metastatic colorectal cancer is typically associated with a poor prognosis with the majority of patients dying within two years from diagnosis, resulting in a five-year survival rate of only 12.8% (*13–15,19,23,30*). Therapeutic options currently available rely on three cytotoxic chemotherapies, fluoropyrimidine (5-FU, capecitabine) (*16,24,25,27,31–32*), oxaliplatin, and irinotecan (*28,33*), and recently on the monoclonal antibodies cetuximab (second-line setting) or bevacizumab (first-line treatments and after progression) depending on the KRAS mutation (*26,29,30,34–36*).

The choice of initial therapy should be tailored to individual needs of the patients, to toxicity profiles of each regimen and to the potential impact of initial therapy on later phases of the treatment. The central goal is to optimize survival, time without toxicity from chemotherapy, and quality of life. The National Cancer treatment guidelines, published by the Lebanese Ministry of Health, define the most recent protocols to be adopted taking in consideration of ASCO (American Society of Clinical Oncology) and ESMO (European Society for Medical Oncology) results. The intensification of the treatment (tri-therapy, with or without monoclonal antibodies) is reserved for resectable colorectal cancer patients and the adjunction of bevacizumab was validated in Lebanon, since 2006 and after 2012, beyond progression with a significant improvement in overall survival. However, the drug's high cost and non-availability (difficulties in reimbursement), make it indicated only in aggressive disease as first-line setting, and is mostly used in second/third-line treatment as maintenance therapy to prevent relapses.

Although patients ≥ 65 years of age represent the majority of patients with metastatic colorectal cancer (*35,37*), the mean age at diagnosis in this study was 60.5 years, which might be due to the young age of the cohort (range 26–89 years). Median overall survival was reported in the study as 20.8 months, which was inferior to that reported by Saltz et al. (2008), and Crystal, Tree and Cremolini et al. (2015), where overall survival after the administration of targeted therapy was significantly increased (from 24 months to 30 months) (*22,38*).

Survival increases as patients with metastatic colorectal cancer are exposed to all available agents, but this benefit comes at high cost, which exceeds commonly accepted cost-effectiveness thresholds (*24*). Furthermore, our estimates only include drug costs, representing a conservative estimate of total treatment expense. Patients

who are treated with 5FU/LV, oxaliplatin, irinotecan or with monoclonal antibodies have longer survival compared to 5FU/LV alone but higher costs. These results are similar to an analysis of salvage chemotherapy in platinum refractory ovarian cancer, which found that second-line monotherapy came at an ICER of $57 000/DLY, but the benefits of second-line doublet therapy and third-line monotherapy came at unacceptably high incremental cost (*25*). Whether the benefits are worth the costs clearly depends on the stakeholder; patients with advanced cancer may perceive greater value than healthy patients, policymakers, insurers, and physicians (*8,9,27,28*).

This study comprehensively analyzed clinical effectiveness and associated medical costs with the use of chemotherapy alone or chemotherapy + targeted agents in patients with metastatic colorectal cancer. We found that the health care costs of colorectal cancer treatment increased significantly with advanced disease, especially for the second-line setting, which is most likely attributable to the use of new drug regimens and protocols (Table 4). Our goal was not to compare "competing" regimens such as FOLFOX and FOLFIRI, which are both acceptable first-line treatment strategies (*27*), but instead to study the impact of sequential progress (new chemotherapy and antibodies) on the overall cost of managing metastatic colorectal cancer. We found that similar treatment sequences had similar life expectancies, suggesting that the costs are not affected by the sequence in which the drugs are used, but rather the effectiveness of the overall treatment strategy.

At the present time, patients with metastatic colorectal cancer are typically treated with a first-line chemotherapy regimen that is continued until documented disease recurrence. Upon progression, patients are switched to a regimen with demonstrated activity on refractory disease. This pattern of treatment continues until patients show progression of their disease and then are switched to non-cross resistant therapy. The last therapies can be changed until all five classes of active agents have been tried.

In patients who were previously treated with the same chemotherapy regimen (first-line included), the addition of targeted therapy to this regimen allowed a response rate of 14% (vs 18%), a disease control rate of 33% (vs 18%) and a stabilization of 19% (vs 0%), suggesting that molecular therapy may circumvent resistance to conventional chemotherapy by allowing a more efficient delivery of chemotherapeutic agents. Tumor vasculature is structurally and functionally abnormal, which results in a heterogeneity in tumor blood flow with interstitial hypertension, hypoxia and acidosis. Hypoxia could therefore make tumour cells resistant to several cytotoxic drugs by interfering with the penetration of these drugs throughout the tumour (*34,39*). This phenomenon was not observed when cetuximab (anti-EGFR antibody) was added to bevacizumab and chemotherapy; on the contrary, it had a possible deleterious effect (*31–33,40–44*). This study also found that patients, specifically the elderly with more than one metastatic site, had higher costs while patients with only one progression or only one line of therapy had lower costs.

Costs connected with metastatic colorectal cancer, primarily those associated with chemotherapy and targeted medications, represent a significant percentage share of total costs. The cost of chemotherapy rose from 6.9% of total costs in 2004 to 8.1% in 2008, and the cost of targeted medications rose from 4.8% in 2004 to 9.4% in 2008. Costs connected with metastatic colorectal cancer were $9 978 per month. Ferro et al. determined that there was growth in the total costs of metastatic colorectal cancer treatment from 1996 onwards, specifically due to increased choice among possible medications, and targeted medications have substantially increased the cost of treating metastatic colorectal cancer (*37,45*). Most studies that provide estimates of the long-term cost of colorectal cancer were conducted in the United States of America (*6–9,46–48*), but to our knowledge, there are no such studies in Lebanon and in the Middle East in general.

It was also noticed that patients with comprehensive insurance (health maintenance organizations and indemnity insurance plans) had lower costs than non-insured participants. The oncological treatment for metastatic disease in 2014 is less toxic and more effective but more expensive (because of the use of monoclonal antibodies). The addition of multiple lines of protocols, mainly targeted and biological agents, to the backbone of chemotherapy, allows better overall survival and PFS (*49*).

Limitations

The sample size in this study is too small to make any definitive recommendations or suggest a change in practice guidelines, therefore collaboration with other cancer centers across the country and generate more data could be subjected to pre-defined rigorous statistical analysis. In addition, official Lebanese tariffs for the year 2013 were the only ones considered. Concerning the screening, there was no National colorectal survival screening strategy or education awareness programme; the screening with fecal occult blood testing is rarely practiced and gastroenterologists recommend and perform screening colonoscopy on an erratic and opportunistic basis.

Many other variables (not found to be significantly associated to death or RECIST in our study such as mutations, histology, differentiation, treatment duration, and types of metastases) may influence time to death or disease progression, but we could not add them in the analysis because of large number of missing values. Differing organization of health systems and different practice patterns and settings made the transferability of country specific results not always possible, so further studies specific to Lebanon are needed.

All drugs are given intravenously in fixed vial sizes, and the total wastage of all drugs that remained in vials at the end of the infusion for each patient was not assumed. Our analysis did not consider indirect costs such as work loss resulting from chemotherapy, tax payer's perspective or direct costs such as transportation to the hospital.

Despite the limitations of this cohort study, the results are useful in presenting the pattern of care of patients with colorectal cancer in a real-life perspective. This approach may be complementary to results from clinical trials since it is more representative of routine clinical practices. This type of study may also represent useful information within the scope of medical-decision making.

Conclusion

This study is, to our knowledge, the first to investigate the real costs of healthcare in patients with a diagnosis of mCRC and receiving systemic therapy (chemotherapy or biotherapy), considering both costs per treatment cycle and total costs per patient based on the Lebanese perspective of the situation. Moreover, it should be standard practice to discuss the option of chemotherapy with patients while outlining the potential toxicities. Analysis of the cost-effectiveness of treatments, including financial and physical costs of toxicities, is becoming increasingly important and strategies to optimize this are vital. We need to balance efficacy of treatment, costs involved with the short- and long-terms toxicities to create a truly Lebanese standard of care for adjuvant colon cancer.

Acknowledgements

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Competing interests: None declared.

Prise en charge des patients atteints d'un cancer colorectal métastatique dans les hôpitaux libanais et coût direct associé : étude de cohorte multicentrique

Résumé

Contexte : Pour le cancer colorectal métastatique, une série de nouveaux traitements sont apparus durant la dernière décennie, mais leur utilisation dans la pratique clinique courante et leurs coûts ne sont pas bien documentés

Objectifs : La présente étude a évalué l'efficacité clinique de ce type de traitements sur les patients atteints de cancer colorectal métastatique dans les unités oncologiques libanaises et en a estimé les coûts.

Méthodes : Une étude de cohorte prospective a été menée sur des patients atteints de cancer colorectal métastatique au cours de la période 2008-2013. Le type de prise en charge médicale, la survie globale et les coûts totaux des traitements du diagnostic jusqu'au au décès ont été décrits. L'analyse des coûts a été réalisée sur la base des tarifs de 2013 en dollars US.

Résultats : Cent soixante-dix-neuf patients métastatiques ont été sélectionnés, dont 84,9 % présentaient une atteinte de type cancer colorectal métastatique. Le suivi moyen entre le diagnostic et le décès ou le dernier contact avec le patient était de 34,8 mois. Environ 49,7 % étaient encore en vie à la dernière date de suivi. Trois lignes de traitement représentaient 4,5 %, 39,6 % et 55,9 % des cas, avec une durée moyenne de 14,5, 11,4 et 14,6 mois respectivement ; 73,2 % des patients ont bénéficié d'un traitement ciblé. La survie globale médiane était de 20,8 mois. Le coût total moyen des médicaments s'élevait à USD 22 256 chez les patients recevant un traitement standard seulement, alors que le coût passait à USD 80 396 après l'ajout du traitement ciblé. Le coût total moyen global a été estimé à USD 64 805 par patient (min. USD 3 703 ; max. USD 304 086).

Conclusions : Le traitement ciblé associé au traitement standard est très répandu au Liban pour les maladies métastatiques et le coût médical associé est substantiel. Cette étude est la première à montrer l'efficacité clinique et les coûts d'un traitement ciblé chez des patients atteints de cancer colorectal métastatique.

علاج مرضى سرطان القولون المستقيمي النقيلي في المستشفيات اللبنانية والتكلفة المباشرة المرتبطة بها: دراسة أترابية متعددة المراكز

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الخلاصة

الخلفية: بالنسبة لمرض السرطان القولوني المستقيمي النقيلي، ظهرت سلسلة من العلاجات الجديدة في العقد الأخير ولكن لم يُوثق استخدامها في الممارسات السريرية الروتينية وتكاليفها بشكل كافٍ.

الأهداف: قيَّمت هذه الدراسة الفعالية السريرية لعلاج مرضى سرطان القولون المستقيمي النقيلي في وحدات علاج الأورام اللبنانية، وقدَّرت تكاليف هذا العلاج.

طرق البحث: أُجريت دراسة أترابية استباقية على مرضى سرطان القولون المستقيمي النقيلي في الفترة بين عامي ٢٠٠٨ و٢٠١٣. وجرى توضيح نوع العلاج الطبي والمعدل الإجمالي للبقاء وإجمالي التكاليف بداية من التشخيص حتى الوفاة. وأُجري تحليل للتكاليف باستخدام التسعيرات بالدولار الأمريكي من عام ٢٠١٣.

النتائج: تم اختيار ١٧٩ مريضًا بالأمراض النقيلية حيث وُجد أن ٨٤,٩٪ منهم مصابين بسرطان القولون المستقيمي. وبلغ متوسط مدة المتابعة بداية من التشخيص حتى الوفاة أو الحصول على أحدث المستجدات ٣٤,٨ شهرًا. وكان حوالي ٤٩,٧٪ لا زالوا على قيد الحياة في آخر موعد للمتابعة. وتم استخدام ثلاثة خطوط للعلاج مع ٤,٥٪ و٣٩,٦٪ و٥٥,٩٪ حيث بلغ متوسط مدة المتابعة ١٤,٥ و١١,٤ و١٤,٦ شهرًا على التوالي. واستفاد ٧٣,٢٪ من المرضى من العلاج المستهدف. وبلغ متوسط المعدل الإجمالي للبقاء ٢٠,٨ شهرًا. وبلغ متوسط إجمالي تكاليف الأدوية ٢٢٢٥٦ دولارًا أمريكيًا مع المرضى الذين يحصلون على علاج معياري فقط، بينما ارتفعت التكاليف إلى ٨٠٣٩٦ دولارًا أمريكيًا بعد إضافة العلاج المستهدف. وقُدِّر متوسط إجمالي التكلفة العالمية ٦٤٨٠٥ دولارًا أمريكيًا لكل مريض (بحد أدنى ٣٧٠٣ دولارًا أمريكيًا؛ بحد أقصى ٣٠٤٠٨٦ دولارًا أمريكيًا).

الاستنتاجات: يعد العلاج المستهدف المرتبط بالعلاج المعياري شائعًا بكثرة في لبنان بين المرضى بالأمراض النقيلية، وتعد التكلفة الطبية للعلاج مرتفعة. وتعد هذه الدراسة هي الأولى من نوعها التي توضح الفعالية السريرية وتكاليف العلاج المستهدف بين مرضى سرطان القولون المستقيمي النقيلي.

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Prevalence and sociodemographic determinants of contraceptive use among women in Oman

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Abstract

Background: The fertility rate in Oman is high, as found elsewhere in Arab countries. The government of Oman has made considerable improvements in providing contraceptive methods in response to growing demand.

Aims: This study aimed to find out the prevalence of contraceptive usage and determine the sociodemographic determinants of its use among married Omani women.

Methods: A cross-sectional survey was carried out in 12 health centres which were randomly selected from each county (Wilayat) in Muscat region. A total of 400 women aged 18–49 years old who had not reached menopause were subjected to a face-to-face interview. Information was obtained on sociodemographic characteristics and family planning practice.

Results: Majority of women (n=397; 99.2%) had heard about family planning. More than half (n=225; 56.3%) knew about family planning and only three (0.8%) did not know its meaning. The contraceptive pill was the most common known method (n=383; 95.8%), while vaginal cream was the least recognized method (n=67; 16.8%). Most of the participants (n=307; 76.8%) reported previous use of these methods and 54% (n=214) were current users. Withdrawal was the most frequently used method (n=70; 32.7%) and breast-feeding was the least used method (n=3; 1.4%). Contraception use increased significantly with age ($P < 0.005$), duration of marriage ($P < 0.005$) and high monthly income ($P < 0.005$).

Conclusions: Health care providers play a key role in providing information and education about family planning. Efforts are recommended in educating couples and promoting the use of the different family planning methods.

Keywords: correlates, contraception, family planning, fertility, Oman

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Introduction

"Family planning allows people to attain their desired number of children and determines the spacing of pregnancies" (*1*); it is achieved through the use of contraceptive methods and the treatment of infertility. The contraceptive prevalence is "the percentage of women who are currently using, or whose sexual partner is currently using, at least one method of contraception, regardless of the method used. It is usually reported for married or in-union women aged 15 to 49" (*2*). Birth spacing and the use of contraception is of high importance for both mother and child. Studies have confirmed that healthy pregnancy timing and spacing are essential to improve infant and maternal health (*3*).

In Oman, the Birth Spacing Programme was initiated in 1994 and was considered a fundamental part of the country's Maternal and Child Health (MCH) services. The main objective of the programme was to offer a variety of contraceptive methods to allow women to space births by three years or more, and thus improve the well-being of both child and mother. Birth spacing services are available through primary health care and extended health centres throughout Oman and form a crucial part of MCH services.

Muscat Governorate has 29 health centres and three polyclinics. Each of these health centres serves a population of approximately 20 000 to 30 000 patients. The birth spacing clinics in these health centres are well developed in terms of a birth spacing register, appointment system and trained family physicians and nurses. The Ministry of Health (MoH) provides a wide range of free birth spacing methods to all Omani women who wish to plan their pregnancies, including condoms, hormonal contraceptives such as progesterone-only pills, combined oral contraceptive pills, injectables and implants, and intrauterine contraceptive devices. The provision and management of this service is regulated by a well-structured guidelines, the result of which the total fertility rate has dropped significantly from 7.84 before 1990 to 4.0 in 2016 (*4–6*). The current fertility rate is similar to a number of other countries of the region, but high compared to Europe and North America (*7*). In addition, other important health indicators have also dropped dramatically over the same period, including maternal mortality rate (from 22 to 13.4), infant mortality rate (from 29 to 9.2) and under 5 mortality rate (from 35 to 11.7) (*6*).

A study published in 2004 indicated that the unmet contraception need for Omani women was nearly 25% (*8*).

This decreased significantly with educational level and employment (i.e. empowered women were more likely to use contraception). However, this study did not include the health information and demographics of women and if they are able to achieve their reproductive intentions (*8*). The current study therefore aimed to assess the prevalence of contraceptive usage and socio-demographic determinants of its use among married Omani women in Muscat region.

Methods

A multicentric, cross-sectional survey was carried out in the primary health centres from September 2014 to September 2015. There are six counties (Wilayat) in Muscat Governorate with a total of 29 health centres. The number of health centres varies from one county to another based on the size of the target population. The current study included 12 health centres, which were randomly selected from each county in Muscat Governorate. All married Omani women aged 18–49 years old who had not reached menopause, attending the health centres for various reasons, were subjected to a questionnaire by a face-to-face interview. Women who did not speak Arabic or English, those with learning difficulties, and those with no time to complete the questionnaire were excluded from the study.

Estimation of sample size

According to the 2010 census, women of reproductive age (15–49 years) constituted 28.9% of the Omani population. Census data provide the total population of each region without detailed age and sex distribution. The proportion of women of reproductive age has been estimated as 28.9% of the region's population. The sample size (n) has been estimated using the Epi-info software [r]. The estimated number of women of reproductive age in Muscat Governorate is 125 678. The rate of contraception use (41.3%) among women exposed to the risk of pregnancy reported by previous studies [r] has been used to estimate the sample size with a degree of precision (d) at 0.05 (*8*). The chosen level of confidence is 95% ($Z_{0.05}$ = 1.96) and a design effect (DEFF) of 1. The applied equation using the Epi-info software was:

$$n = [DEFF*Np\ (1-p)]/\ [(d^2/Z^2_{0.05}*(N-1)+p*(1-p)].$$

The total sample size selected equaled 372 women. The number of women selected was proportional to the number of women in each region (Table 1).

Questionnaire and interview

A pre-tested and well-structured questionnaire was used by the authors for data collection. The questionnaire was validated and previously used in two similar studies in Jordan (*9,10*). The questionnaire is divided into two main sections; part one concerns the participants' and husbands' socio-demographic information such as age, level of education, duration of marriage, employment status, and total monthly income. The second part concerns family planning practice and current use of contraception, types used, duration of use, reasons for use, history of side effects, and attitudes towards contraceptive methods. The questionnaire was translated into Arabic and the authors, who are qualified physicians, conducted the face-to-face interviews, which took 15–20 minutes. The participants were selected from the waiting areas and briefed on the objectives of the study when eligible. The researchers were always available to respond to participants' inquiries and comments. A written consent with a statement of confidentiality was taken from all the participants and their privacy was maintained throughout. The study was anonymous and all participants were given a study number, which was used for data analysis.

Ethics approval

Ethical approval for the study was granted by the Medical Research and Ethics Committee of the College of Medicine and Health Sciences at the Sultan Qaboos University, Oman, and by the Research and Ethics Committee of the Directorate General of Health Services, Ministry of Health, Oman.

Statistical analysis

The data analysis was carried out using IBM SPSS statistics version 23. Descriptive statistics were used to describe the sample characteristics. For categorical variables, frequencies and percentages were reported. The Pearson's χ^2 test (or Fisher's exact tests for low cell frequencies) was used to test significance when appropriate and a *P*-value ≤ 0.05 was considered significant. For continuous variables, mean and standard deviation were used to present the data.

Table 1: Distribution of population (Omani) in Muscat Governorate by region from 2010 census and number of women selected

County (Wilayat)	Suggested number of health centres	Omani population	Estimated number of women (age 15–49 years)	Number of estimated sample
Muttrah	2	50 739	14 664	43
Bowsher	2	77 973	22 534	67
Al Seeb	4	197 569	57 097	169
Al Amerat	2	48 768	14 094	42
Muscat	1	20 585	5949	18
Qurayyat	1	39 238	11 340	34
Total	12	407 006	125 678	372

Results

A total of 400 married women from 12 different primary health centres were approached to participate in this study. All of them agreed to take part in the study leading to a response rate of 100%. The mean age of the participants was 31 ± 6 years and the marriage duration median was 6 ± 6 years. The socio-demographic characteristics of the participants are shown in Table 2.

Almost all of the participants (n=397; 99.2%) reported that they had heard about family planning. More than half (n=225; 56.3%) knew that family planning is to plan for pregnancy before it happens and only 0.8% (n=3) did not know its meaning. The pill was the most commonly known contraception method (n=383; 95.8%), followed by intrauterine contraceptive device (n=373; 93.3%), withdrawal (n=373; 93.3%), condom (n=365; 91.3%), and injectable (n=362; 90.5%), while vaginal cream (n=67; 16.8%), emergency contraception (n=57; 14.3%) and hormonal patch (n=4; 1%) were the least heard about methods (Figure 1). The participants mentioned several sources of information on family planning methods, where medical services were the most common source (n=222; 56%) followed by family members (n=153; 38%) and friends (n=88; 22%).

Among the 397 women who knew about contraceptive methods, three quarter (n=307; 76.8%) reported an ever use of these methods while around half (n=214; 54%) were current users of contraception. Among the current users of contraception, withdrawal was the most commonly used method (n=70; 32.7%) while breastfeeding was the least used method (n=3; 1.4%) (Figure 2). Most of the current users (n=167; 78%) stated that birth spacing is the main reason for using contraception followed by medical indications and conditions (n=49; 23%) and physician's advice (n=19; 9%). A small proportion (n=17; 8%) stated that their family size was complete. Only 4% (n=8) used contraceptives due to family economics.

The majority of current users of contraception (n=132; 62%) reported experiencing one or more side effects from the method used. The most reported side effects in general were back pain (n=40; 30%), period disturbances (n=37; 28%), mood swings (n=30; 22%), weight gain (n=28; 21%), headache (n=26; 20%), and interruption of intercourse (n=26; 20%). Almost one third (n=91; 30%) of those reported an ever use of contraception (n=307) fell pregnant while using a particular method. These methods were withdrawal (n=41; 45%), the pill (n=15; 16%), and condoms and calendar (n=13; 14%). However, women who were non-current users of contraception were either pregnant (n=80; 43%), wanted more children (n=35; 19%) or were convinced that they do not need contraception (n=32; 17%).

Table 2: Distribution of sociodemographic characteristics of participants (n=400)

Characteristic	Categories	Frequency
Wilayat	Muttrah	44 (11%)
	Bowshar	68 (17%)
	Al Seeb	171 (42.8%)
	Al Amerat	42 (10.5%)
	Muscat	28 (7%)
	Qurayyat	47 (11.8%)
Age	≤25 years	139 (34.8%)
	26–29 years	216 (54%)
	30–39 years	45 (11.3%)
Husband's age	≤25 years	20 (5%)
	26–35 years	215 (53.8%)
	36–45 years	132(33%)
	46–55 years	25(6.3%)
	>55 years	8 (2%)
Employment status	Employed	213 (57.8%)
	Unemployed	169 (42.3%)
	Missing	18(4.5%)
Educational level	Primary	39 (9.8%)
	Secondary	171(42.8%)
	High	190 (47.5%)
Duration of marriage	<5 years	139 (34.8%)
	5–10 years	216 (54%)
	>10 years	45 (11.3%)

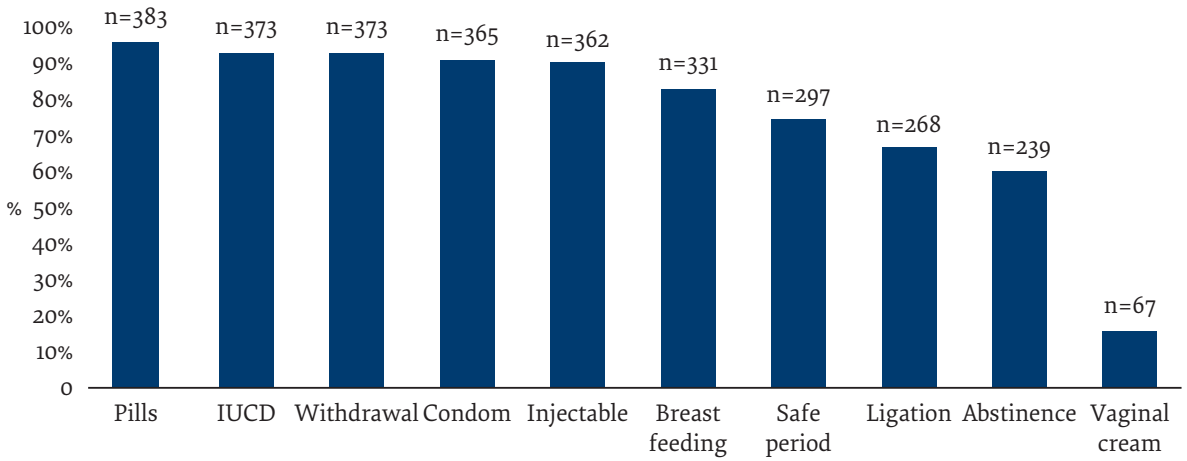
Women's practice and attitude towards the use of family planning methods

A chi square test was used to examine the effects of participants' categorical characteristics on their use of family planning methods. Women's age was a significant determinant of contraception use, and women over the age of 40 years (n=28; 82%) were more likely to use contraception compared to women who were less than 25 years old (n=10; 19%) ($P < 0.005$). Likewise, the duration of marriage was a significant factor towards the practice of family planning; more women who were married for over 15 years (n=38; 84%) were in favour of using contraception compared to those married for 5–15 years (n=131; 61%) and those married for less than 5 years (n=43; 31%) ($P < 0.005$). Furthermore, the more the family earns the more likely women were users of contraception ($P < 0.005$).

In contrast, women's employment did not have a significant role in women's current use of contraception ($P = 0.94$). Women's level of education was found to be of borderline significance towards their family planning practice; 57% (n=108) of women with high level of education were users of contraception compared to only 46% (n=18) of users among women with primary level of education ($P = 0.045$). Similarly, husband's age had a borderline significance ($P = 0.048$) (Table 3).

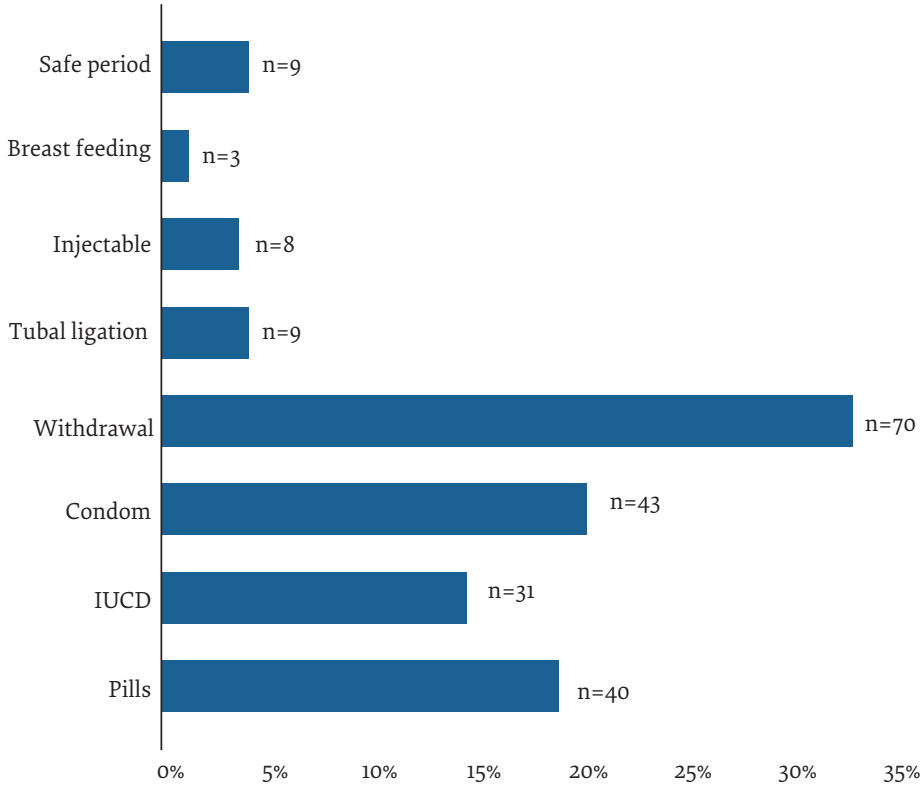
The majority of husbands of the surveyed women (n=364; 91%) had a positive attitude towards family planning. The great majority of women who have used contraception (n=316; 79%) have discussed the method with their partners and most of them (n=246; 78%) agreed on its use. Only 2% (n=6) of women had to hide the use of contraception from their partners.

Figure 1: Knowledge of family planning methods among women (n=397)



Multiple answers were allowed thus percentages do not add up to 100%

Figure 2: Distribution of family planning methods among current contraception users (n=214)



Discussion

The present study has shown that the vast majority of women (n=397; 99.2%) have heard about family planning methods and 56.3% knew its meaning. The most commonly known methods were pills, intrauterine device and withdrawal. This is fairly similar to what is reported in the Middle East region (*8–10*). Even though the vast majority of women knew about the different methods available, one third of the current users preferred the withdrawal method. This suggests that many are motivated to space their children but are using less effective traditional methods. Hence, it is important for the health services to find ways to encourage them to use more effective long acting methods. Participants relied mainly on healthcare services for information on family planning methods as well as family and friends. This clearly demonstrates the important role of health services in providing advice on family planning and influencing the use of contraception. Therefore, health education on this matter should be provided extensively and simultaneously to clients and the community as a whole and stress on

Table3: Use of family planning (FP) methods by different sociodemographic characteristics of study sample (n=400)

Variable	Users of FP (n=212) n (%)	Non-users of FP (n=188) n (%)	P-value**
Age (years)			
≤25	10(18.5)	44(81.5)	**<.005**
26–29	64(51.2)	61(48.8)	
30–39	110(58.8)	77(41.2)	
40–49	28(82.4)	6 (17.6)	
Husband's age (years)			
≤25	6 (30.0)	14(70.0)	**0.048***
26–35	108(50.2)	107(49.8)	
36–45	77(58.3)	55(41.7)	
46–55	18(72.0)	7 (28.0)	
>55	<5(n<5)	5(62.5)	
Years of marriage			
<5	43(30.9)	96(69.1)	**<0.005**
5–15	131(60.6)	85(39.4)	
>15	38(84.4)	7(15.6)	
Education level			
Primary	18(46.2)	21(53.8)	**0.045**
Secondary	96(69.1)	85(49.7)	
High	108(56.8)	82(43.2)	
Employment status			
Employed	127(55.0)	104(45.0)	**0.354**
Unemployed	85(50.3)	84(49.7)	
Monthly income (OMR)			
<500	39(51.3)	37(48.7)	**0.003**
500–1000	61(42.1)	84(57.9)	
1000–2000	53(63.1)	31(36.9)	
>2000	59(62.1)	36(37.9)	

**Age categories (45–55) and (>55) were combined; **Pearson chi square test P value.*

the availability of modern methods. Medical staff should have a positive attitude and must encourage their clients to talk more freely about these methods.

This study showed that 76.8% of women have previously used contraception and 54% are currently using them. According to the United Nations (UN) estimates of contraceptive prevalence, 64% of women in almost all regions of the world are using some form of contraception. However, the rates of contraception usage in the Arab countries vary considerably. The usage of contraception was found to be high in countries such as Bahrain (66.0%), Lebanon (63.0%) and Jordan (61.8%), while lower rates have been reported in other countries such as Yemen (37.6%) and Saudi Arabia (36.8%). In comparison to other geographic areas, contraceptive use is much higher in Eastern Asia (82%), Northern Europe (77%), North America (75%), and South America (75%) and particularly low in Africa in general (33%); Sub-Saharan Africa (28%), Middle Africa (23%) and Western Africa (17%) (*11*). This variation could be attributed to a variety of reasons including cultural, social, religious and political.

In the current study, women who were using contraceptives have mainly used the withdrawal method (33.0%) followed by condoms (20.0%), pills (18.7%) and intrauterine contraceptive devices (IUCDs) (14.5%). Most of the participants mentioned that birth spacing is the main reason for using contraception and few admitted that they have completed their families and did not want more children. This finding varies from what is observed in neighbouring countries where women relied heavily on modern methods (*12–13*).

Globally, it is estimated that 57% of women of reproductive age use a modern method of family planning (*11*). In addition, this study reveals that 45% of women who relied on the withdrawal methods admitted getting pregnant while on the method compared to only 16% of women on the pill. These figures are alarming and warrant urgent action to increase awareness on modern

contraceptive methods and the options available. Proper counseling and health education about the correct use of contraception methods are very important and should be stressed by health services and medical workers, particularly when using the pill, which has a failure rate of less than 1% if used correctly (*4*). Furthermore, further research is required to assess the actual reasons why women are reluctant to use modern methods. A possible reason is that these estimates are probably lower than those in reality since couples can easily obtain these contraceptive methods over the counter without a prescription and/or simply from the widely accessible private clinics. In addition, couples might be avoiding these methods because of the possible side effects. This is very likely as a large proportion of women on contraception (62%) admitted experiencing some side effects including back pain, period disturbances and mood swings.

Women's age, duration of marriage and family income were significant determinants of contraception use. The usage of contraception was more common among women older than 40 years, married for more than 15 years, and with higher household income. These findings are consistent with studies reported in Qatar (*12*), United Arab Emirates (*13*), Jordan (*9*) and Saudi Arabia (*14*). This is expected since the older the woman and the longer the marriage, the more likely that fertility goals have been achieved and the desired number of children reached. Moreover, high income influences economic development and leads to easy availability of information and accessibility to these methods, thus increasing the potential of using these means.

In addition, women's employment did not have a significant association with the use of contraception. This result is in contrast to the findings reported by a previous study conducted in Oman as well as other studies in the region (*14*). Interestingly, women's level of education and husband's age were found to be of borderline significance, even though similar studies in the region have shown its importance in determining the use of contraception (*9,12,13*). However, several studies conducted in India showed that education was not positively associated with contraceptive use (*15,16*). In general, education level and employment status are two important indicators of women's empowerment, hence increasing the likelihood of their use of family planning methods (*8,17*).

Limitations

The reported proportion of contraceptive users might be overestimated as women in the extended community are expected to use clinical services and family planning less frequently and the types of contraceptive methods available are diverse

Furthermore, this study was conducted in one region of the country (Muscat) and the transferability of the findings on the determinants of contraceptive use to the wider population is unknown, given their diverse educational, employment and social status to that of Muscat region. Therefore further comprehensive research will be required in order to compare the current findings to that of the wider Omani population

Conclusion

The vast majority of women were aware of family planning, and the pill, IUCD, condom and withdrawal were well-known methods. Approximately 77% of the participants had previously used contraception and 54% are current users. The participants preferred mainly traditional methods over modern methods available. A significant association was noticed between contraception use and women's age, duration of marriage and monthly family income. Healthcare providers play a key role in providing information and education about family planning. Efforts are recommended to encourage and promote the use of different birth spacing methods among women of reproductive age and increase public awareness on the important Maternal and Child Health (MCH) services.

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Prévalence du recours à la contraception et déterminants socio-démographiques associés chez les femmes à Oman

Résumé

Contexte : Le taux de fécondité à Oman est élevé, à l'instar de la situation dans d'autres pays arabes. Le gouvernement d'Oman a effectué d'importantes améliorations dans la mise à disposition de méthodes contraceptives afin de répondre à la demande croissante.

Objectifs : La présente étude avait pour objectif d'établir la prévalence du recours à la contraception et de cerner les déterminants socio-démographiques associés chez des femmes omanaises mariées.

Méthodes : Une étude transversale a été réalisée dans 12 centres de santé choisis aléatoirement dans chaque circonscription (Wilayat) de la région de Mascate. Au total, 400 femmes âgées de 18 à 49 ans n'ayant pas atteint la ménopause ont passé un entretien face-à-face. Des informations ont été obtenues sur les caractéristiques socio-démographiques et les pratiques de planification familiale.

Résultats : La majorité des femmes (n=397; 99,2 %) avaient entendu parler de la planification familiale. Plus de la moitié d'entre elles ((n=225; 56.3 %) connaissaient la planification familiale et seulement trois d'entre elles (0,8 %) ne savaient pas ce dont il s'agissait. La pilule était la méthode la plus couramment connue (n=383; 95.8 %) tandis que la crème vaginale était la méthode la moins reconnue (n=67; 16.8 %). La plupart des participantes (n=307; 76,8 %) ont déclaré avoir déjà utilisé ces méthodes et 54 % (n=214) étaient des utilisatrices au moment de l'étude. Le retrait était la méthode la plus fréquemment utilisée (n=70 ; 32,7 %) et l'allaitement au sein était la méthode la moins utilisée (n=3 ; 1,4 %). L'utilisation des contraceptifs augmentait de façon significative avec l'âge (p < 0,005), la durée du mariage (p < 0,005) et un revenu mensuel élevé (p < 0,005).

Conclusions : Les prestataires de soins de santé jouent un rôle clé dans l'information et l'éducation sur la planification familiale. Des efforts sont recommandés pour éduquer les couples et promouvoir l'utilisation des différentes méthodes de planification familiale.

معدل انتشار استخدام وسائل منع الحمل والعوامل المحددة له من الناحية الاجتماعية والسكانية بين النساء في عُمان

رحمة محمد الكندي، هناء حارب السمري

الخلاصة

الخلفية: يعد معدل الخصوبة في عُمان مرتفعًا، كما وُجِدَ ذلك أيضًا في البلدان العربية الأخرى. قامت حكومة عُمان بإدخال تحسينات كبيرة في توفير وسائل منع الحمل استجابة للطلب المتزايد.

الأهداف: هدفت هذه الدراسة إلى معرفة معدل انتشار استخدام وسائل منع الحمل وتحديد العوامل المحددة له من الناحية الاجتماعية والسكانية بين النساء العُمانيات المتزوجات.

طرق البحث: أُجريت هذه الدراسة الاستقصائية المقطعية في ١٢ مركزًا صحيًا تم اختيارهم بعشوائية من كل ولاية في محافظة مسقط. وخضعت ٤٠٠ امرأة تتراوح أعمارهن بين ١٨ و٤٩ عامًا ولم ينقطع الطمث لديهن إلى مقابلة شخصية مباشرة. وتم الحصول على معلومات بشأن الخصائص الاجتماعية والسكانية وممارسة تنظيم الأسرة.

النتائج: سمعت أغلب النساء (n=٣٩٧؛ ٩٩,٢٪) عن تنظيم الأسرة. وعرفت ما يزيد عن نصفهن (n=٢٢٥؛ ٥٦,٣٪) معلومات بشأن تنظيم الأسرة، وثلاثة نساء فقط (٠,٨٪) لم يعرفن معنى هذا المصطلح. وكانت الوسيلة الأكثر شيوعًا هي حبوب منع الحمل (n=٣٨٣؛ ٩٥,٨٪)، بينما الكريم المهبلي كان الوسيلة الأقل شيوعًا (n=٦٧؛ ١٦,٨٪). وذكرت معظم المشاركات (n=٣٠٧؛ ٧٦,٨٪) استخدامهن لهذه الوسائل في السابق، بينما لا تزال (n=٢١٤؛ ٥٤٪) يستخدمن هذه الوسائل في الوقت الحالي. وكان العزل (قذف خارج الرحم لمنع الحمل) هو الوسيلة الأكثر استخدامًا (n=٧٠؛ ٣٢,٧٪)، والرضاعة الطبيعية كانت الوسيلة الأقل استخدامًا (n=٣؛ ١,٤٪). ويزداد استخدام وسائل منع الحمل بشكل كبير مع التقدم في العمر (P (الاحتمالية) < ٠,٠٠٥)، ومع طول فترة الزواج (P < ٠,٠٠٥)، ومع الدخل الشهري المرتفع (P < ٠,٠٠٥).

الاستنتاجات: يؤدي مقدمو الرعاية الصحية دورًا رئيسيًا في تقديم المعلومات والتثقيف بشأن تنظيم الأسرة. ويُوصى ببذل مزيد من الجهود لتثقيف الأزواج وتعزيز استخدام وسائل تنظيم الأسرة المختلفة.

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Low-risk planned caesarean versus planned vaginal delivery at term: early and late infantile outcomes

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Abstract

Background: Understanding the impact of delivery mode on neonatal morbidity becomes essential in the context of rising Caesarian delivery rates.

Aims: We aimed to compare the selected outcomes in neonates born by low-risk planned Caesarian delivery versus planned normal vaginal delivery (NVD).

Methods: This prospective cohort study examined early, and late neonatal complications among 1071 neonates born through low-risk planned Caesarian delivery and 1367 neonates born through planned NVD, in Fars, Islamic Republic of Iran, during 2012–2014.

Results: Gestational age of neonates born through Caesarian delivery was significantly lower than their counterparts in NVD group. Accordingly, babies' birth weights were 3166 (±442.4) grams in Caesarian delivery group and 3213 (±454.8) grams in NVD group. Normal skin colour at birth was more prevalent in the Caesarian delivery group compared to the NVD group (85% vs. 81.3%, P = 0.04). No significant differences were detected between the two groups regarding birth trauma, birth height and head circumference, and developing infection, icterus and convulsion during neonatal period. Also, height and weight at two years of age did not significantly differ in both groups.

Conclusion: The results of this study show that neonates born by Caesarian delivery and NVD had the same early and late outcomes.

Keywords: vaginal delivery, caesarean delivery, outcome, cohort study, Iran

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Introduction

The rate of caesarean delivery has increased worldwide over the past decades (*1–3*). There has been a rise in Caesarian deliveryrate in the United States of America from 1996 to 2004 when 1.2 million women (29.1% of all births) had Caesarian delivery (*4*). In many high-income countries it has exceeded 30% over the past decades. In Germany from 1990 to 2010 it doubled from 15.7 to 31.9% of all births (*5*). Moreover; worldwide estimates of Caesarian delivery at maternal request are 6–8% in Northern Europe, 11.2% in the United States, 17.3% in Australia and 70% in Brazil (*6*). A significant rise in Caesarian delivery rate from 14.3% in 1979 to 85.3% in 2009 in the Islamic Republic of Iran has also been reported, although this was a hospital-based report (*7*).

Caesarian delivery has been considered as a global burden for many years (*8*) and has been the most common surgical procedure performed on American women (*9*). A higher risk of infant morbidity including breastfeeding complications (*10*), infections and respiratory distresses and even maternal bleeding has been reported to be associated with Caesarian delivery (*11*). Moreover, compared to planned vaginal delivery, planned CD was related to higher rate of severe maternal morbidity (*12*).

However, according to studies, Caesarian delivery is selected to avoid certain medical conditions such as fetal distress, fear from urinary sequellas, and anal incontinence (*13,14*). A main concern is whether the rise in the Caesarian delivery rate is the reason for the fall in perinatal mortality during the past decades (*3*). Although Caesarian delivery is more expensive than normal vaginal delivery (NVD) (*15*), it is more common in the private sector (*16*). Also, the rate of Caesarian delivery went beyond the rate recommended by the World Health Organization (WHO); i.e., 15% of all deliveries, over the past decades.

The decision to choose Caesarian delivery or NVD based only on the emotional status of a pregnant woman is due to evidence indicating a lack of difference in complication rates between Caesarian delivery and NVD patients (*17*). Within these controversies, understanding the impact of delivery mode on neonatal morbidity and mortality becomes essential in the context of rising Caesarian deliveryrates. Therefore, the present study aims to compare the neonates born by low-risk planned Caesarian delivery and those born by planned NVD regarding selected neonatal outcomes.

Methods

Study design and population

This prospective cohort study is a part of the cohort study which has been started since 2012 in Fars, the fifth most populated province in the Islamic Republic of Iran (*18*). Aiming to compare neonatal outcome of low-risk planned Caesarian delivery and planned NVD, we included mothers whose infant was alive and delivery date was after 37^{+0} weeks, and who had no history of maternal or fetal complications. We also excluded those whose date of delivery was influenced by maternal or fetal complications, including premature labour pain, ruptured membrane, fetal intra-uterine growth retardation or meconium staining. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1397.464) (*19*).

Data collection

In this article we used data collected during fetal period, 2, 6 and 24 months after birth. Data were collected during pregnancy included demographic, medical history and obstetric and gynaecological history of mothers. The checklist used 2 months after delivery consisted of two main parts: the first part asked questions regarding mode of delivery and whether it was planned and if the mode of delivery was NVD. The next question was concerning type of NVD; routine NVD, physiologic NVD, NVD in water, or painless NVD in which intrathecal analgesic is used routinely. Those mothers who experienced Caesarian delivery were asked about the reason of Caesarian delivery.

In the next part of the study, we asked mothers to answer questions regarding neonatal outcomes based on the infants' health card, vaccination card as well as the diary we had given the mothers in the first phase of the study (during pregnancy). In this part, we asked about infant's weight, height and head circumference at birth as well as presence of congenital anomalies (if any). Since APGAR is not recorded in either the health card or the vaccination card, we had to ask mothers about the neonate's skin colour, crying, and limbs' movement after birth and the place the neonate was kept immediately after birth; i.e. next to mother or in a neonatal intensive care unit (NICU)/neonatal ward. We also asked about birth trauma including bone fracture(s) and/or dislocation(s) and sculpt hematoma, if the child had developed icterus, infection, and convulsion in the neonatal period. The history was considered positive if the diagnosis was confirm by a paediatrician, or the infant was admitted to hospital due the mentioned problems. We also asked if breastfeeding was started within two hours after delivery, and the duration of exclusive breastfeeding.

After the infants passed their 6 and 24 months, the mothers were contacted and asked about any ailments/disease(s) their children had developed that necessitated a visit to a doctor. Also details of infants' feeding including duration of exclusive breastfeeding and weaning were requested, as well as information about any disease(s) confirmed by a physician, any hospital admissions, reason(s), and frequency and duration of each hospitalization (if any).

Statistical analysis

Statistical analyses were performed using SPSS statistical software, ver. 18.0 (SPSS Inc., Chicago, IL: USA). All the participants were categorized into two groups; those who had planned NVD and those who had planned CD. All the comparisons were made between these two groups. Independent *t*-test was used to compare the quantitative variables, while chi-square test or Fisher's exact test was employed to compare the qualitative ones. All differences with *P*-values less than 0.05 were considered as statistically significant. The data were reported as mean ± standard deviation (SD) and frequency (percentage) as indicated.

Results

Two months after delivery, we interviewed 4577 out of the 6922 mothers (66.1%) who had participated in the first phase of the cohort study, which have been started in 2012 (*17*). We found that 72 respondents (1.8%) had experienced either still birth (32; 0.7%) or neonatal mortality (40; 0.8%). Among the rest of the respondents (4505 mothers) whose pregnancies resulted in live births, 1250 mothers (27.7%) had emergency delivery — either NVD or Caesarian delivery. Hence, of the 3255 mothers who had experienced planned deliveries, 1457 had planned NVDs (44.8%) and 1798 had planned Caesarian deliveries (55.2%). Considering that we aimed to compare neonatal outcome of low-risk pregnancies, we excluded all planned deliveries in which mother and/or the fetus was considered high risk by the maternity care provider. Therefore, data of 1367 low-risk planned NVD and 1071 low-risk planned Caesarian delivery were analyzed. Different indications of Caesarian delivery have been illustrated in Figure 1.

Comparison of maternal and neonatal characteristics between the two groups – low-risk planned NVD versus low-risk planned Caesarian delivery – is presented in Table 1, which indicates that the mean age of mothers in NVD group was slightly lower than that of the Caesarian delivery group (26.5 vs. 28.4 years; $P < 0.001$), which was not clinically significant. Besides, the mothers who had Caesarian delivery were more likely to have a higher education level and significantly more likely to be employed (12.1%) compared to their counterpart in NVD group (5%; $P < 0.001$). A remarkably higher proportion of mothers who gave birth through Caesarian delivery had received maternity care at private clinics (46.4% vs. 20.3%, $P < 0.001$). Also, they are more likely to have a history of infertility (9.2% vs. 401%; $P < 0.001$), abortion/stillbirths (23.1% vs. 16.5%; $P < 0.001$), and children with physical and/or mental disabilities (2.4% vs. 0.9%; $P = 0.003$). Yet, health insurance coverage was similar in both groups ($P = 0.4$). In Caesarian delivery group, 9 (0.8%) twin and 1 (0.1%) triplet deliveries were reported, while in NVD group just 1 (0.1%) twin pregnancy was mentioned. No significant

Table 1: Comparing maternal and neonatal characteristics the group who had planned NVD versus those who had C-section

Characteristics	Planned NVD N = 1367	Planned C-section N = 1071	*P*-value
Maternal			
Age (years)	**26.5 (± 4.9)**	**28.4 (± 4.7)**	**< 0.001***
No. of previous children	**2 (0-6)**	**2 (0-5)**	**0.04†**
Up to secondary school	704 (51.5)	331 (31)	< 0.001§§
High school diploma	470 (34.4)	405 (37.7)	
Undergraduate degree	186 (13.6)	317 (29.6)	
Postgraduate degree	7 (0.5)	18 (1.7)	
Employment			
Employed	69 (5)	130 (12.1)	< 0.001§
Unemployed (housewife/student)	1298 (95)	942 (87.9)	
Place of received maternity care			
Private clinics	277 (20.3)	497 (46.4)	**< 0.001§**
Governmental Clinics	1090 (79.7)	574 (53.6)	
Having insurance	**1270 (92.9)**	**992 (92.6)**	**0.4§**
Positive history of infertility	**56 (4.1)**	**99 (9.2)**	**< 0.001§**
Positive history of abortion/stillbirth	**225 (16.5)**	**247 (23.1)**	**< 0.001§**
Having children with physical and/or mental problem	**12 (0.9)**	**26 (2.4)**	**0.003§**
Place of delivery			
Hospital	1165 (85.3)	1026 (95.9)	< 0.001§§
Maternity hospital	188 (13.6)	45 (4.1)	
Facility centre	1 (0.1)	0	
Gynaecologist clinic	8 (0.6)	0	
At home	6 (0.4)	0	
Sex			
Male	675 (49.4)	543 (50.7)	0.55§§
female	691 (50.5)	532 (49.3)	
Ambiguous	1 (0.1)	0	
Number of tones			
Single tone	1366 (99.9)	1061 (99.1)	0.007§§
Twin	1 (0.1)	9 (0.8)	
Triplet	0	1 (0.1)	
Congenital anomalies	**11 (0.8)**	**7 (0.7)**	**0.8§**

**Independent T test*

†Two-independent samples tests

§Chi-square test

§§Fisher's exact test

P values less than 0.05 is considered significant.

Data are reported as mean (± standard deviation), Median (min - max), and frequency (%); NVD = normal vaginal delivery

difference was observed between the NVD and Caesarian delivery groups regarding the infants' gender.

Comparison of the immediate neonatal outcomes between planned NVD and low-risk planned Caesarian delivery groups is presented in Table 2. Accordingly, gestational age (39.2 vs. 38.4 weeks; $P < 0.001$) and birth weight (3213 vs. 3166 grams; $P < 0.001$) were significantly higher in the NVD group compared to the Caesarian delivery group. However, the differences were not clinically significant. No statistical differences were found between the two groups in neonates' head circumference and height at birth. The newborns delivered through Caesarian delivery were more likely to have normal skin colour compared to those delivered via NVD (85% vs. 81.3%; $P = 0.04$). However, no significant differences were detected between the neonates of two groups regarding grade of crying, limbs movement vigor, respiration, skull hematoma, birth trauma, and place of care after birth (next to mother or in NICU/neonatal

Figure 1: **Flowchart of participants' recruitment**

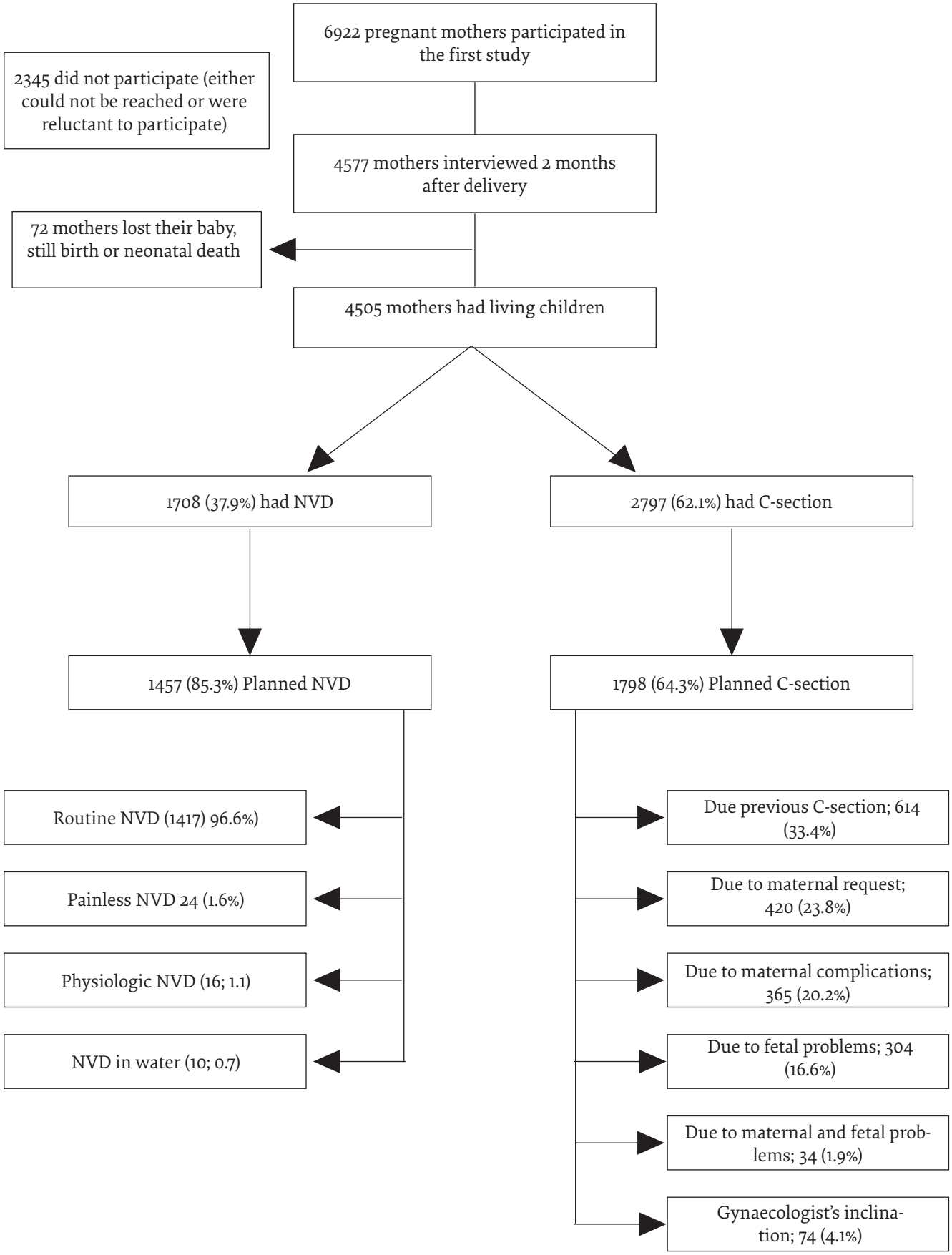

Table 2: Comparing immediate neonatal outcomes in planned NVD versus planned C-Section

Neonatal outcomes	Planned NVD N = 1367	Planned C-section N = 1071	*P*-value
Gestational age at birth (weeks)	39.2 (± 1.2)	38.4 (± 1.2)	< 0.001*
Birth weight (grams)	3213 (± 454.8)	3166 (± 442.4)	0.01*
Height at birth (centimetres)	50.2 (± 2.8)	50 (± 3.0)	0.1*
Head circumference	34.8 (± 1.6)	35 (± 1.5)	0.2*
Place of care after birth			
Next to mother	1283 (93.9)	997 (92.9)	0.4§
NICU or neonatal ward	84 (6.1)	77 (7.1)	
Crying			
Vigorous	1302 (95.2)	1034 (96.5)	
Weak	54 (4.0)	32 (3.0)	0.2§
No crying	11 (0.8)	5 (0.5)	
Skin colour			
Pink/normal	1112 (81.3)	910 (85.0)	
Reddish	221 (16.2)	144 (13.4)	0.04§
Cyanotic/pale	34 (2.5)	17 (1.6)	
Movement			
Vigorous	1349 (98.7)	1060 (99)	
Weak	14 (1.0)	10 (0.9)	0.5§§
Poor/none	4 (0.3)	1 (0.1)	
Respiration			
Normal	1331 (97.4)	1043 (97.4)	
Nasal oxygen	27 (2.1)	25 (2.3)	0.3§
Intubation	9 (0.6)	3 (0.3)	
Birth trauma			
Skull hematoma	5 (0.4)	2 (0.2)	0.3§§
Skull deformity	1 (0.1)	0	0.6§§
Clavicle	5 (0.4)	3 (0.3)	0.5§§
Femur	0	2 (0.2)	0.2§§

**Independent t test*

§Chi-square test

§§Fisher's exact test

P values less than 0.05 is considered significant.

Data are reported as mean (± standard deviation), or frequency (%); NVD = normal vaginal delivery

Table 3: Comparing early neonatal outcomes in both groups; planned NVD versus planned C-Section

Neonatal outcomes	Planned NVD N = 1367	Planned C-section N = 1071	*P*-value
Icterus			
Developing icterus	469 (34.3)	381 (43.9)	0.52§
Start day	3.8 (± 2.3)	3.6 (± 2.5)	0.6*
Duration of icterus	1.6 (± 0.6)	1.7 (± 0.5)	0.07*
Blood exchange	3.0 (0.6)	0	
Phototherapy	323 (69.3)	270 (70.9)	
Medication	14 (3.0)	9 (2.4)	0.58§
Home remedy &/ breastfeeding	221 (16.2)	144 (13.4)	
Photo and breast feeding cessation and medication	124 (26.4)	100 (26.2)	

Table 3: Comparing **early neonatal outcomes in both groups; planned NVD versus planned C-Section (*concluded*)**

Neonatal outcomes	Planned NVD N = 1367	Planned C-section N = 1071	*P*-value
Infection			
Developing infection	75 (5.5)	70 (6.5)	0.3§
Start day	5.1 (± 4.7)	6.8 (± 8.1)	0.09*
Hospitalization due to infection[6]	16 (21.3)	7 (10.0)	0.2§
Duration of admission	2.1 (± 1.4)	2 (± 1.4)	0.8*
Convulsion			
Developing convulsion	13 (1.0)	12 (1.1)	0.8§§
Start day	7.8 (± 2.6)	9.9 (± 2.5)	0.7*
Hospitalization due to convulsion[66]	4 (30.8)	3 (25.0)	0.1§

**Independent T test*

§Chi-square test

§§Fisher's exact test

[6]The proportion of neonates admitted due to infection

[66]The proportion of neonates admitted due to convulsion

P values less than 0.05 is considered significant.

Data are reported as mean (± standard deviation), or frequency (%); NVD = normal vaginal delivery

Table 4: Comparing outcomes during the first two years of life in children born through planned NVD versus planned C-section

Late outcomes	Planned NVD N = 1367	Planned C-Section N = 1071	*P*-value
Height at 2 years old (centimetres)	84.6 (± 4.0)	85.7 (± 3.9)	0.1*
Weight at 2 years old (kilogrammes)	11.6 (± 3.6)	11.8 (± 1.5)	0.3*
Hospital admission/paediatrician visit			
The child visited by a doctor (for reasons other than check-up)	471 (34.5)	332 (31.0)	0.07§
History of hospital admission	202 (14.8)	183 (17.1)	0.1*
Duration of total hospitalization[δ]	5 (1-105)	4 (1- 63)	0.9**
Congenital anomalies/diseases			
Presence of at least one congenital anomaly/diseases	113 (8.3)	91 (8.5)	0.4§
	n (n/113*100)	**n (n/91*100)**	
G6PD deficiency	79 (69.9)	73 (80.2)	
Thalassaemia minor	16 (14.1)	5 (5.5)	
Musculoskeletal (club foot, polydactyly)	4 (3.5)	2 (2.2)	
Cardiac problems	2 (1.8)	7 (7.7)	
Oro-pharyngeal problems	3 (2.6)	3 (3.3)	
Urogenital problems	3 (2.6)	1 (1.1)	
Down Syndrome	2 (1.7)	1 (1.1)	
Ophthalmic problems	1 (0.8)	2 (2.2)	
Other problems	7 (6.2)	3 (3.3)	
Developing diseases during the first two years			
Dermatologic problems	43 (3.2)	34 (3.1)	0.9§
Respiratory problems including asthma	19 (1.4)	13 (1.2)	0.6§§
Nephrology problems	4 (0.3)	2 (0.2)	0.7§§
Neurologic problems	4 (0.3)	1 (0.1)	0.5§§
Musculoskeletal problems	1 (0.1)	1 (0.1)	0.9§§

**Independent T test*

***Mann-Whitney Test*

[δ]Duration of total hospitalization= summation of number of hospital admission duration of each admission*

§Chi-square test

§§Fisher's exact test

P values less than 0.05 is considered significant.

Data are reported as mean (± standard deviation), or frequency (%); NVD = normal vaginal delivery

Table 5: Comparing breast feeding pattern in children born through planned NVD versus planned C-Section

Breast feeding	Planned NVD N = 1367	Planned C-section N = 1071	*P*-value
Initiation of breast feeding			
Was not started at all	1 (0.1)	3 (0.2)	< 0.001§
Within 2 hours after delivery	1316 (96.3)	1001 (93.5)	
Within 3 three days after delivery	50 (3.6)	67 (6.3)	
Duration of breast feeding (months)	***19.9 (± 6)***	***18.8 (± 8.1)***	***< 0.001****
Less than 7 days after birth	20 (1.5)	19 (1.7)	
The first month of life	16 (1.2)	37(3.4)	
Up to 2 months old	15 (1.1)	20 (1.8)	
Up to 4 months old	35 (2.4)	62 (5.9)	
Up to 6 months old	46 (3.2)	56 (5.2)	< 0.001§§
Up to 1 year old	54 (4.0)	67 (6.3)	
Up to 1.5 years old	149 (11)	92 (8.6)	
Up to 2 years old	1032 (75.5)	716 (66.9)	
For more than 2 years	0	2 (0.2)	
Duration of exclusive breast feeding (weeks) 20.9 (± 1.6)		***19.8 (± 2.2)***	***< 0.001****
Never	15 (1.1)	16 (1.5)	
Less than one month	29 (2.1)	45 (4.2)	0.01§§
Less than 4 months	101 (7.4)	107 (10)	
4 months	212 (15.5)	195 (18.2)	
6 months	1010 (73.9)	708 (66.1)	

**Independent T test*

§Chi-square test

§§Fisher's exact test

P values less than 0.05 is considered significant.

Data are reported as mean (± standard deviation), or frequency (%); NVD = normal vaginal delivery

ward). Neonatal outcomes are described in Table 3. Neonatal complications did not statistically differ in those born through Caesarian delivery and those in NVD group; i.e., icterus (P = 0.52), infection (P = 0.3) and convulsion (P = 0.8).

Certain aspects of health status during the first two years of life were also compared between the two groups and the results are presented in Table 4. Accordingly, no significant difference was found between the two groups regarding height (P = 0.1) and weight (P = 0.3) at two years of age. Nevertheless, compared to the children born through Caesarian delivery, those born through NVD had more frequently developed ailment/disease(s) for which they had to be visited by a doctor during the first two years of life (34.5% vs. 31%; P = 0.07). However, those born through Caesarian delivery had been more frequently hospitalized (17.1% vs. 14.8%; P = 0.1). Yet, the two groups were similar regarding presence of congenital anomalies/diseases (P = 0.4) and developing nephrological (P = 0.7), dermatological (P = 0.9), neurological (P = 0.5), musculoskeletal (P = 0.9), and respiratory problems including asthma (P = 0.6).

According to what had been recorded by mothers in their diaries, breastfeeding had never been started for three infants (0.2%) in Caesarian delivery group and one infant (0.1%) in NVD group. The reason was multiple congenital anomalies in oropharynx of the infants. Breastfeeding was more likely to be started within two hours after delivery in the neonates born through NVD compared to neonates in Caesarian delivery group (96.3% vs. 93.5%). For the remainder of the neonates, breastfeeding was started within three days; 3.6% in NVD group comparing to 6.3% in Caesarian delivery group. Duration of breastfeeding was also longer in the NVD group compared to the Caesarian deliverygroup (19.9 vs. 18.8 months, P < 0.001). Also, the duration of exclusive breastfeeding was significantly (P < 0.001) higher in NVD group compared to Caesarian delivery infants; 20.9 weeks (± 1.6) vs. 19.8 weeks (± 2.2), respectively.

Discussion

Appropriateness of Caesarian delivery and NVD for pregnant women has been widely debated. In this cohort study, we compared maternal and neonatal characteristics as well as immediate, early, and late neonatal complications among the women who delivered their babies by NVD and Caesarian delivery. The mean age of the mothers was lower in the NVD group than in the Caesarian

delivery group. In addition, the mothers in the CD group were more likely to be more educated and be employed. Besides, a significantly higher proportion of Caesarian deliveries were performed at private settings. Similar results were also obtained in other studies (*15*,*16*).

The results of our study demonstrated a higher birth weight in the infants delivered by NVD. However, birth weight was reported to be higher in the Caesarian delivery neonates than in the NVD ones (*20*). The longer gestational age in the NVD group in our study could be a reason for fetal weight gain. Also, the infants born through Caesarian delivery were more likely to have normal pink skin at birth. However, no significant differences were detected between the two groups regarding birth height, place of care after birth (next to mother or in neonatal ward), type of crying, movement, respiration, skull hematoma, and birth trauma. Some studies have reported that mode of delivery could not be related to birth trauma (*21*), but it has also been reported that Caesarian delivery is protective against birth trauma (*22*). Other studies have reported an association between Caesarian delivery and newborn's serious respiratory morbidity (*23*,*24*), respiratory distress (*25*), and transient tachypnea (*26*). In addition, delivery by Caesarian deliveryhas been identified as a risk factor for child asthma (*27*), respiratory morbidity, and longer NICU stay. Conversely, delivery by Caesarian delivery was reported not to be associated with the subsequent development of asthma, allergic rhinitis, or atopic dermatitis in Korean children (*28*).

Evaluation of early neonatal outcomes in the groups under study did not show any differences between the two groups regarding development of icterus, infection and other early neonatal complications. This was in agreement with the results of another study indicating no significant difference between NVD and Caesarian delivery neonates concerning neonatal complications (*29*). In a Chinese study, short-term maternal outcomes were similar in NVD and Caesarian delivery mothers, and Caesarian delivery women had even better neonatal benefits (*30*). In contrast, a Swedish study reported that Caesarian delivery either without medical indication or in emergency situations were associated with higher risks for maternal and neonatal morbidity (*11*).

The study results also revealed no significant difference between the two groups with respect to height and weight at the end of the second year of life. In contrast, Caesarian delivery has been reported as a risk factor for child obesity (*27*). Moreover, a systematic review reported a strong association between Caesarian delivery and increased offspring Body Mass Index (BMI), overweight, and obesity in adulthood (*31*). Compared to vaginally born infants, Caesarian delivery infants have different timing, composition, and acquirement of intestinal flora, which may contribute to intestinal microbial composition in the first year of life, causing obesity and other health outcomes (*27*).

There was no significant difference between the NVD and Caesarian delivery group regarding the rate and length of hospital admission. This was in contrast to the results of other studies, showing higher newborn hospitalization for vaginally born neonates (*20*). Nevertheless, similar to the present research, that study demonstrated no significant difference between Caesarian delivery and NVD born infants with regard to duration of hospital stay. In has been shown that in preterm births,Caesarian delivery significantly increases the risk of longer neonatal length of hospital stay compared to NVD (*32*). Our study results also indicated no significant differences between the two groups regarding dermatological, nephrological, spinal cord, and musculoskeletal problems.

In this study, a slightly higher but significant proportion of the Caesarian delivery neonates did not start breastfeeding at all. Duration of breastfeeding was higher in the NVD group than in the Caesarian delivery group. Compared to the Caesarian delivery infants, a significantly higher proportion of the NVD infants had six-month exclusive breastfeeding. These findings were consistent with those of other studies (*29*,*32*,*33*).

The main strength of this study is that all data have been collected prospectively in a cohort study by trained research assistants and we did not use retrospectively collected hospital data. The limitation of the study is that we had to rely on mothers' claims, although they were trained to write all important events regarding their baby as well as themselves in the notebook given to them during their.

Conclusion

The results of this study show that neonates born by Caesarian deliveryand normal vaginal delivery had the same early and late outcomes. Also Caesarian delivery neonates were more likely to have normal pink skin at birth. However, breastfeeding habits were better among NVD neonates. Considering the controversies reported in studies on Caesarian delivery and NVD outcomes, more research is needed to evaluate the short-term and long-term effects of Caesarian delivery.

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Césarienne planifiée à faible risque par rapport à l'accouchement vaginal planifié à terme : résultats précoces et tardifs pour l'enfant

Résumé

Contexte : Comprendre l'impact du mode d'accouchement sur la morbidité néonatale devient essentiel dans le contexte de la hausse des taux de césariennes.

Objectifs : Nous voulions comparer certains résultats chez les nouveau-nés par césarienne planifiée à faible risque par rapport à l'accouchement vaginal normal planifié.

Méthodes : L'étude de cohorte prospective a examiné les complications néonatales précoces et tardives chez 1071 nouveau-nés suite à une césarienne planifiée à faible risque et 1367 nouveau-nés suite à un accouchement vaginal planifié, dans la province de Fars, République islamique d'Iran, entre 2012 et 2014.

Résultats : L'âge gestationnel des nouveau-nés par césarienne était significativement inférieur à celui de leurs homologues du groupe des accouchements vaginaux normaux. Par conséquent, le poids à la naissance des bébés était de 3166 (±442,4) grammes dans le groupe des césariennes et de 3213 (±454,8) grammes dans le groupe des accouchements vaginaux normaux. La couleur normale de la peau à la naissance était plus fréquente dans le groupe des césariennes que dans l'autre groupe (85 % contre 81,3%, p = 0,04). Aucune différence significative n'a été détectée entre les deux groupes en ce qui concerne les traumatismes à la naissance, la taille de naissance et le périmètre crânien, ainsi que le fait de contracter une infection, un ictère et les convulsions durant la période néonatale. De plus, la taille et le poids à l'âge de deux ans ne différaient pas de façon significative dans les deux groupes.

Conclusion : Les résultats de cette étude montrent que les nouveau-nés par césariennes et par accouchement vaginal normal présentent les mêmes résultats précoces et tardifs.

الولادة القيصرية منخفضة المخاطر المُخطط لها مقابل الولادة المهبلية في موعدها المُخطط لها: مخرجات الولادة المبكرة والمتأخرة بالنسبة للرضع

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الخلاصة

الخلفية: أصبح فهم تأثير نوع الولادة على المراضة بين الأطفال حديثي الولادة ضروريًا في سياق معدلات الولادة القيصرية المتزايدة.

الأهداف: هدفنا إلى مقارنة المخرجات المحددة بين الأطفال حديثي الولادة الذين وُلِدوا من خلال الولادة القيصرية منخفضة المخاطر المُخطط لها مقابل الولادة المهبلية الطبيعية المُخطط لها.

طرق البحث: بحثت هذه الدراسة الأترابية الاستباقية مضاعفات الولادة المبكرة والمتأخرة بين ١٠٧١ طفلاً حديث الولادة وُلِدوا من خلال الولادة القيصرية منخفضة المخاطر المُخطط لها و١٣٦٧ طفلاً حديث الولادة وُلِدوا من خلال الولادة المهبلية الطبيعية المُخطط لها، في مدينة فارس، جمهورية إيران الإسلامية، في الفترة بين عامي ٢٠١٢ و٢٠١٤.

النتائج: كان العمر الحملي للأطفال حديثي الولادة الذين وُلِدوا من خلال الولادة القيصرية أقل بكثير من العمر الحملي للأطفال حديثي الولادة الذين وُلِدوا من خلال الولادة المهبلية الطبيعية. لذلك، كان الوزن عند الولادة ٣١٦٦ (±٤٤٢,٤) جرامًا في فئة الأطفال الذين وُلِدوا من خلال الولادة القيصرية، و٣٢١٣ (±٤٥٤,٨) جرامًا في فئة الأطفال الذين وُلِدوا من خلال الولادة المهبلية الطبيعية. وكان لون البشرة الطبيعي عند الولادة أكثر انتشارًا بين فئة الأطفال الذين وُلِدوا من خلال الولادة القيصرية مقارنة بفئة الأطفال الذين وُلِدوا من خلال الولادة المهبلية الطبيعية (٨٥٪ مقابل ٨١,٣٪، P (الاحتمالية) = ٠,٠٤). ولم يُلاحظ أي اختلافات جوهرية بين الفئتين فيما يتعلق برضح الولادة، والطول عند الولادة، ومحيط الرأس، والإصابة بالعدوى، واليرقان والاختلاجات في فترة الولادة الحديثة. ولم يختلف الطول والوزن عند عمر السنتين اختلافًا كبيرًا بين الفئتين.

الاستنتاجات: توضح نتائج هذه الدراسة أن الأطفال حديثي الولادة الذين وُلِدوا من خلال الولادة القيصرية منخفضة المخاطر والولادة المهبلية الطبيعية لديهم نفس حصائل الولادة المبكرة والمتأخرة.

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Methicillin resistant *Staphylococcus aureus* outbreak in a neonatal intensive care unit

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Abstract

The global and national burden of communicable and noncommunicable diseases continues to rise, thus making access to Healthcare workers (HCWs) colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) may pose transmission risk to vulnerable patients including neonates. This study reports an MRSA outbreak in a level-II neonatal intensive care unit (NICU) of a secondary care hospital in Pakistan. Once identified, an infection control team from the parent hospital visited the facility, risk factors were listed and infection control measures taken to control the outbreak. Screening cultures of NICU staff and environmental cultures from NICU were obtained for the presence of MRSA. Five neonates were positive for MRSA; one HCW was found to be colonized with MRSA, the antibiogram pattern of which matched with that of the outbreak strain. Decolonization of colonized HCWs and re-deployment from NICU to outpatient department were taken and the outbreak was declared over once no further MRSA cases were identified. Identification of an outbreak situation is the cornerstone for its control and multiple measures taken simultaneously help in curbing the outbreak. Although an epidemiological link was established with the HCW, a molecular link could not be proven.

Keywords: outbreak; MRSA; NICU; health care worker, Pakistan

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Introduction

Neonatal intensive care unit (NICU) patients are at high risk of acquiring colonization and infection by Methicillin-resistant *Staphylococcus aureus* (MRSA) (*1*). MRSA in NICUs was first reported in 1981 (*2*); since then, the organism has been reported regularly in this age group and several outbreaks have been reported globally (*3,4*). Hospital-acquired MRSA infections in neonates can cause a variety of diseases including blood stream infections, meningitis, brain abscess, pneumonia, osteomyelitis, infective arthritis, skin and soft tissue infections, conjunctivitis and endocarditis, and leading to serious morbidity and mortality. The role of health care workers (HCWs) has been cited in the nosocomial transmission of MRSA (*5*) and poor infection control practices have also been implicated in its acquisition and transmission (*6*). Routine decolonization of asymptomatic HCWs is not recommended unless they have been identified as a source of an outbreak (*7*). There are several other studies that report cessation of nosocomial MRSA outbreaks after proper decolonization of HCWs (*8–10*).

This is a report of an MRSA outbreak in a neonatal care unit of a local secondary care hospital during the period 6 November to 31 December 2013. The source of this outbreak was traced to a HCW and the aim of this observational study is to highlight the importance of implementation of infection prevention /control measures and limitations for controlling an outbreak.

Ethical considerations

The study was provided an exemption by the Ethics Review Committee of the Aga Khan University, Karachi, Pakistan (ERC # 4693-Pat-ERC-17).

Outbreak report

Setting

The MRSA outbreak occurred in a secondary care hospital of the Aga Khan University Hospital (AKUH), Karachi, Pakistan. The facility conducts around 3000 deliveries annually. The hospital has 45 beds in total with level-I and -II neonatal intensive care units. There are about 600 admissions to the NICU annually. Level-II NICUs provide care to neonates of ≥ 32 weeks or ≥ 1500 g that have physiological immaturity or neonates that are moderately ill with problems that are expected to be resolved. Level-I NICUs provide neonatal resuscitation at every delivery and care for neonates born at 35–37 weeks that are physiologically stable.

The level-II NICU of secondary care hospital comprises a single room with one entrance/exit door, used by both mothers and HCWs. A small feeding area where mothers feed their babies is also present in the same room. Because of limited space, there was often overcrowding. There are three incubators and two cots in the NICU and has the capacity of admitting five neonates in total. However, because of limited beds and increased

load, this number is often exceeded resulting in a mismatch between patient and nurse numbers. Neonates are fed as required and bottles and the weighing machine are disinfected during every shift. Diapers are changed as required.

Staphylococcus aureus was grown on chocolate and sheep blood agar (for blood culture and pus specimen) or cysteine lactose electrolyte deficient agar (for urine specimen). Growth characteristics and colony gram stain were observed. Catalase and slide coagulase tests were performed for preliminary identification followed by tube coagulase according to the standard protocols (*11*). Susceptibility testing was performed as prescribed by Clinical and Laboratory Standards Institute (*12*). The outbreak included a total number of five neonates whom cultures were positive for MRSA.

Index Case

The first neonate was born on 4 November, 2013, in the secondary care hospital by elective caesarean section at 38 weeks due to history of previous caesarean section and gestational diabetes mellitus (mother on insulin). The neonate was shifted to NICU due to transient tachypnea of newborn and grunting; blood culture was sent, which grew MRSA.

The second neonate was admitted the next day (5 November) at 48 hours of life because of jaundice, and had been delivered vaginally at term. Urine culture that was sent as part of workup for jaundice and sepsis was found to be positive for MRSA.

The third neonate was admitted on 21 November, 2013, from a clinic at 48 hours of life because of fever, and had been delivered vaginally at term in hospital and was discharged home on first day of life. In this neonate, MRSA grew in urine culture.

The fourth neonate was admitted on 23 November, 2013, at 26 hours of life because of jaundice and had been delivered vaginally at term and also had MRSA positive in urine culture.

The fifth neonate was delivered by elective caesarean section on 20 November, 2013, and was kept in a well-baby nursery for three days. This neonate was admitted on fourth day of life to the nursery due to fever and excessive crying. The neonate developed intravenous catheter site abscess and a pus culture was sent and reported positive for MRSA.

Initial suspicion of outbreak was made when urine culture of 2nd neonate was reported positive on 7 November, 2013. At this point, in addition to the standard protocol of isolation of colonized or infected neonates, other immediate infection control steps were implemented by nursery staff including strict adherence to hand hygiene by alcohol-based hand sanitizers or soap and water. A check was put on traffic control in the nursery allowing only parents of admitted neonates. Doors were kept locked so that no-one could enter without permission in the nursery, operation theatre and labour room. Protocols were re-emphasized for terminal cleaning of all patient care areas.

On 21 November, 2013, the urine culture of the third neonate was reported positive for growth of MRSA and within 4 days the 4th and 5th neonates were also found to be culture positive. At this point infection control committee members visited the nursery, labour room and operation theatre from which environmental cultures were taken. The rest of the neonates admitted in the nursery were also screened for MRSA during the period of outbreak investigation. In addition, the entire nursery staff was screened. Specimens were taken from their nares, hairline and hands. Extensive training of housekeeping staff, including cleaning of surfaces and frequently touched areas, was stressed. Strict infection control measures were taken during the outbreak and were followed up thereafter. Paramedical staff and physicians of NICU and wards were reinforced to follow proper hand washing techniques and frequency of hand wash as per WHO recommendations (*13*).

Already sick neonates had priority care and new admissions to NICU were suspended until discharge of currently admitted neonates. All neonates with a culture positive for MRSA were placed under contact precautions and isolated to avoid further spread. As the neonates were already on vancomycin, which was changed on the basis of culture report, none deteriorated and were discharged home in a stable condition. On follow-up visits they were found to be healthy.

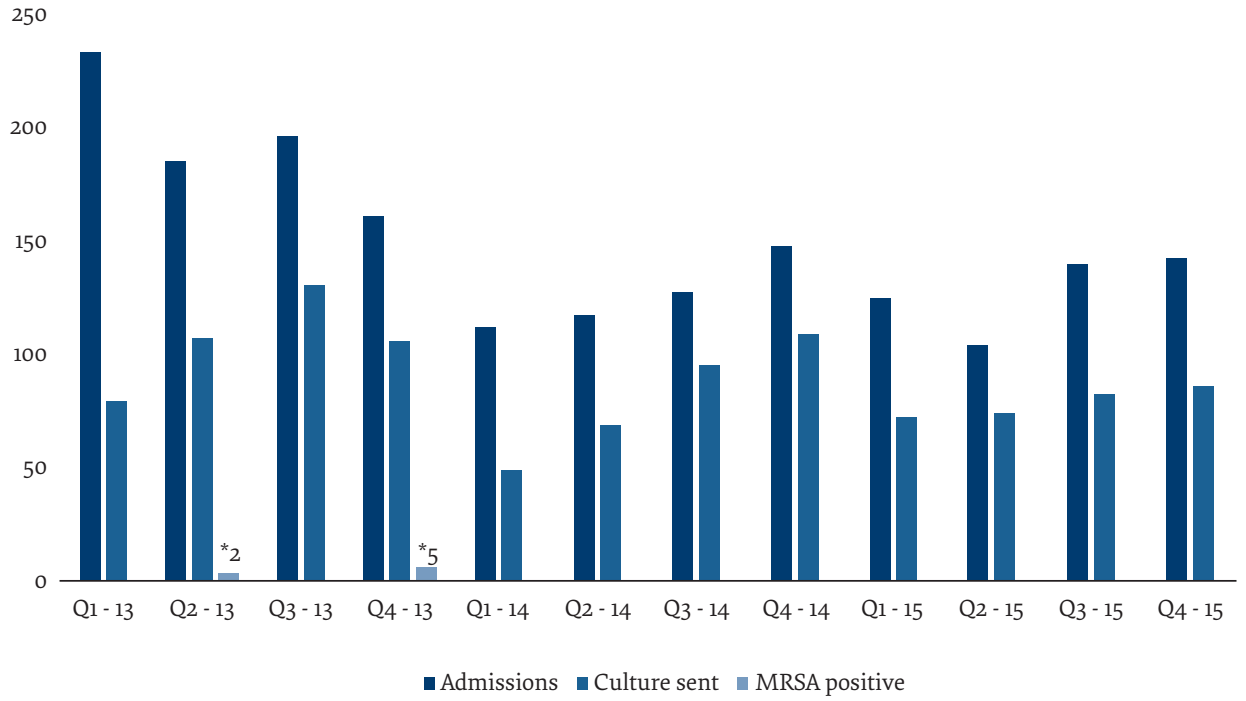
Additional measures implemented included avoidance of overcrowding. To facilitate this, admission has now been limited to its capacity, number of alcohol based hand sanitizers had been increased and placed in between each incubator, and a fixed time had been designated for visitors.

All screening cultures from other admitted neonates as well as environmental cultures were found to be negative. MRSA was detected in nasal cultures of one nurse while remaining staff cultures were found negative. The susceptibility pattern of the MRSA isolated from the HCW was in concordance with the susceptibility pattern of outbreak isolates derived from clinical samples of five neonates (Table 1). The HCW was recommended to have decolonization therapy, which included a five-day course of mupirocin nasal ointment twice a day and daily chlorhexidine bath. She was moved from the nursery to the outpatient clinic, which is considered as a low risk area with minimal patient contact. After the decolonization course, a nares sample was cultured as evidence of clearance from MRSA colonization, which took place 10 days after decolonization therapy and was found negative and the HCW was allowed to carry on with regular duties. The outbreak came to an end after taking all these collective measures and no further cases have been reported since (Figure 1).

Discussion

This MRSA outbreak in a neonatal level-II nursery had been linked to the MRSA colonized HCW. Although molecular typing of MRSA isolate from neonates and staff

Figure 1: MRSA isolation on quarterly (Q1-13 to Q4-15) basis from neonates admitted to nursery from 2013 to 2015.



*Numbers of MRSA positive cases in 2nd and 4th quarters of 2013 are shown above the bars

Table 1: Antibiotic susceptibility pattern of MRSA strains isolated from clinical samples of neonates and screening culture of health care worker.

Antibiotic	Patient-1 (blood culture)	Patient-2 (urine culture)	Patient-3 (urine culture)	Patient-4 (Urine culture)	Patient-5 (Pus culture)	Health care worker (MRSA Screen)
Penicillin	R	NT	NT	NT	R	R
Oxacillin	R	R	R	R	R	R
Gentamicin	S	S	S	I	S	S
Amikacin	S	S	S	S	S	S
Erythromycin	S*	NT	NT	NT	S	S
Clindamycin	S	NT	NT	NT	S	S
Cotrimoxazole	S	S	S	S	S	S
Vancomycin	S	S	S	S	S	S
Ciprofloxacin	S	S	S	S	S	S
Fusidic acid	S	NT	NT	NT	S	S
Tetracycline	S*	S*	S*	S*	S*	S

*MRSA = Methicillin resistant Staphylococcus aureus. S = susceptible. R = resistant. I = intermediate. NT = not tested. * = not reported.*

could not be performed, this remains a plausible explanation as no further cases were reported after the HCW was identified and removed temporarily from direct dealing with patients. Furthermore, the antimicrobial susceptibility pattern of MRSA isolated from the HCW also matched with the MRSA isolates from the neonates.

The epidemiology of MRSA in NICU can be extremely complex because outbreaks can overlap endemic circulation, and tracing the transmission routes is therefore considered to be challenging (14). NICU surveillance data for 2013 shows two MRSA isolates during the second quarter (1.8% out of 107 cultures sent), reflecting the possibility of endemic circulation (Figure 1). However, a sudden rise in the number of MRSA cases during the fourth quarter of 2013 (5 MRSA cases [4.7%] out of 106 culture requests) would fit with an outbreak definition.

Among five MRSA culture positive neonates, one had growth in blood and one in pus aspirate, which was collected from the catheter insertion site, while three neonates had MRSA growth in urine. The clinical condition of first and fifth neonate was consistent with

MRSA sepsis (supported by blood and pus aspirate culture results). In the remaining three cases, the blood culture was reported negative while urine culture grew MRSA. These three neonates were discharged after a short stay in NICU; therefore, evidence for the MRSA sepsis was weak.

Although difficult to prove in retrospect, the positive urine cultures might represent contamination of specimen during collection from the colonized perineal area of neonates. Blood cultures for all three were negative. For the neonate testing positive for MRSA from the blood culture, it could be due to colonization followed by entry into the bloodstream through a minor break in the skin or through colonization of the respiratory tract. Although colonization was a possibility for neonates that had only a positive urine culture for MRSA, vancomycin was added to their treatment regimen.

The literature indicates that in multiple outbreaks, HCWs have been involved in the transfer of MRSA to patients. A review article reported mean nasal MRSA carriage of 4.1% among hospital staff in 104 studies. Furthermore, the same review also described transmission of MRSA from HCWs to patients. One hundred and six studies were evaluated, from which 27 studies demonstrated clear molecular evidence of MRSA transmission from HCWs to patients, while 52 studies where typing was not performed, transmission was considered likely (*5*). Similar to the current report, there are several studies that have reported cessation of an outbreak after proper decolonization of HCWs; however, effects of other simultaneous infection control measures could not be ruled out (*8–10*).

Risk factors for MRSA carriage in HCWs include cutaneous lesions or conditions such as dermatitis, eczema, sinusitis, rhinitis, chronic otitis externa, etc. Work-related factors include work experience, area of service (e.g. medicine, surgery, long-term care facilities), employment in areas where MRSA is endemic, close contact with patients (e.g. wound contact), poor infection control practices (e.g. poor hand hygiene), and high work load. Decolonization with mupirocin ointment in an outbreak setting is recommended for HCWs carrying MRSA (*7*). In the current study the colonized HCW was treated successfully with mupirocin nasal ointment along with chlorhexidine baths. Mupirocin susceptibility testing was not performed for this outbreak of MRSA isolates. However, previously published data from AKUH clinical laboratory show low minimum inhibitory concentrations for MRSA isolates against mupirocin, which helped predict the treatment response in this case (*15*).

Recommendations

We could only establish an epidemiological link of the outbreak with the colonized HCW. Typing of MRSA strains could not be performed and thus a molecular link was not ascertained. It is imperative that infection control measures should be taken prudently at all times. In case of an outbreak, these measures must be re-emphasized and environmental cultures should be taken along with screening of the HCW.

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Competing interests: None declared.

Flambée épidémique de *Staphyloccocus aureus* résistant à la méthicilline dans une unité de soins intensifs néonatals

Résumé

Les agents de santé colonisés par le *Staphyloccocus aureus* résistant à la méthicilline (SARM) peuvent poser un risque de transmission aux patients vulnérables, y compris les nouveau-nés. La présente étude fait état d'une flambée de SARM dans une unité de soins intensifs néonatals (USIN) de niveau II d'un hôpital de soins secondaires au Pakistan. Une fois identifiée, une équipe de lutte contre l'infection de l'hôpital mère a visité l'établissement, y a dressé la liste des facteurs de risque et pris des mesures pour endiguer l'infection en vue de juguler la flambée. Des cultures de dépistage sur le personnel de l'unité de soins intensifs de néonatalogie et des cultures environnementales de l'USIN ont été obtenues pour détecter la présence du SARM. Cinq nouveau-nés étaient positifs au SARM ; un agent de santé a été colonisé par le SARM, dont l'antibiogramme correspondait à celui de la souche de la flambée. La décolonisation des agents de santé colonisés et leur transfert de l'unité de soins intensifs néonatals vers le service de consultation externe ont été réalisés et la flambée a été déclarée terminée lorsque aucun autre cas de SARM n'a été identifié. L'identification de la situation de la flambée est la pierre angulaire de l'action de lutte et de multiples mesures prises simultanément aident à enrayer la flambée. Bien qu'un lien épidémiologique ait été établi avec l'agent de santé, un lien moléculaire n'a pu être prouvé.

حدوث وباء المكورات العنقودية الذهبية المقاومة للميثيسيلين في وحدة الرعاية المركزة لحديثي الولادة

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الخلاصة

قد يُشكِّل العاملون في مجال الرعاية الصحية حاملي العدوى بمكورات عنقودية ذهبية مقاومة للميثيسيلين خطرًا بانتقال المرض إلى المرضى المعرضين للخطر، بما في ذلك الأطفال حديثي الولادة. وتشير هذه الدراسة إلى حدوث وباء المكورات العنقودية الذهبية المقاومة للميثيسيلين في وحدة الرعاية

المركزة لحديثي الولادة على المستوى الثاني التابعة لأحد مستشفيات الرعاية الثانوية في باكستان. وبمجرد تحديدها، قام فريق مكافحة العدوى من المستشفى الأم بزيارة المرفق، وتم إدراج عوامل الخطر واتُخذت تدابير مكافحة العدوى لمكافحة الوباء. وجرى فحص مزارع العينات المأخوذة من العاملين في وحدة الرعاية المركزة لحديثي الولادة، والمأخوذة من بيئة وحدة الرعاية، للتأكد من وجود المكورات العنقودية الذهبية المقاومة للميثيسيلين. ووُجدَ أن خمسة أطفال حديثي الولادة مصابين بالمكورات العنقودية الذهبية المقاومة للميثيسيلين، وعامل رعاية صحية واحد حامل للعدوى، وتطابقَ نمط المقاومة بمخطط المضادات الحيوية مع السلالة المسببة للوباء. وتم علاج عامل الرعاية الصحية الحامل للعدوى، كما نُقل الأطفال بوحدة الرعاية المركزة لحديثي الولادة إلى قسم العيادات الخارجية، وتم إعلان القضاء على الوباء بمجرد التأكد من عدم وجود إصابات أخرى بالمكورات العنقودية الذهبية المقاومة للميثيسيلين. ويعد تحديد وضع الوباء ركنًا أساسيًا في مكافحتها، ويساعد اتخاذ تدابير متعددة فورية في الحدّ من هذا الوباء. ورغم وجود الصلة الوبائية بعامل الرعاية الصحية الحامل للعدوى، تعذر إثبات الارتباط الجزيئي.

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Letter in response to article:

Human development index, maternal mortality rate and under 5 years mortality rate in West and South Asian countries, 1980–2010: an ecological study

Alimohamadi Y; Khodamoradi F; Khoramdad M; Shahbaz M; Esmaeilzadeh F. Human development index, maternal mortality rate and under 5 years mortality rate in West and South Asian countries, 1980–2010: an ecological study. East Mediterr Health J. 2019;25(3):189–196 https://doi.org/10.26719/emhj.18.029

Determinants of maternal and child mortality: some methodological notes

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Sir,

The valuable article recently published in the EMHJ examined the relationship between HDI, maternal and child (under 5 years) mortality in West Asia (*1*). In that paper, descriptive statistics and Spearman correlation coefficient were used for data analysis. There are several methodological points to seem to be debatable.

Firstly, for a comprehensive investigation of health-related socioeconomic factors, not only the HDI indicator but also other determinants of health status (maternal and child mortality) need to be considered. Even if the investigator's goal is not to examine the impact of such factors, their effects should be methodologically controlled. In this regard, there are several factors that have been ignored: skilled birth attendance, vaccination, fertility rate, health services/expenditure, urbanization and etc (*2,3*).

Secondly, regression models are often used to examine the factors affecting health status, referred to as health production function in health economics (*4*). In these models, which can be cross-sectional, time series, or longitudinal, not only all effective factors are assessable and controllable, the coefficients obtained are more reliable. In that study, correlation coefficients that do not have the capabilities of econometric models have been used. So direction of relationship between HDI and mortality indicators is not clear.

In addition to the abovementioned points, in the study by Alimohamadi et al., correlation coefficients have been reported for each individual country (*1*). Given that the number of time points examined from 1980 to 2010 (1980, 1985, 1990, 1995, 2000, 2005 and 2010) was only seven for each country, it seems that the coefficients are not so reliable due to the very small sample size.

In general, an appropriate method could be the use of a panel/longitudinal data model through which all the determinants might be included, the sample size would be increased, and the coefficients would be more reliable.

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Response by authors

Firstly, the main limitation of the current study was the lack of additional information in under studied areas. The mentioned variables such as skilled birth attendance, vaccination, fertility rate, health services/expenditure, and urbanization etc. were not ignored in the current study but the data about such variables were not available in this setting and not accessible to us.

Secondly, the type of current study was an ecological (*1*) or correlational study (*2*), and the main purpose was to determine the correlation between factors under study and not determinant factors of maternal and child mortality. In other words, the regression models are used

when there is a dependent variable and the purpose is to determine the effect of different factors (covariates) on that variable also controlling the confounding factors. This method is used when many variables are available and the main purpose of the analysis is the evaluation of the effect of the covariate on dependent variables, prediction and confounding control (3). However, in the current study the purpose was to determine the correlation between variables under study; we did not have dependent and independent variables. In such a situation, the use of correlation coefficients is more logical.

The correlation coefficient in different ecological studies, where used (4,5), is the main form of analysis. The correlation coefficient assesses the linear relationship between two variables and the amount of this coefficient can differ from -1 to +1. The negative sign indicates the reverse relationship between two variables (by increasing the amount of each variable, the other variable will decrease.) and the positive sign refer to a positive relationship (by increasing the amount of each variable, the other variable will also increase). There are some differences between correlation and linear regression but these differences are not impressive. In testing the hypothesis, the correlation and linear regression gives the same results. So if one's main interested is the *P* value, the difference between correlation and regression is not a concern (6).

Due to the nonparametric distribution of data in the current study, the Spearman correlation coefficient was used. The needed observation for performing the current test is at least 8 to 10 observations for each variable under study, but this test can apply to fewer observations. The disadvantage of a small sample size is an increased effect of chance error, a decrease in the precision of results, and finally affecting nonsignificant results. However, in the current study, all *P* values are significant and therefore a larger sample size or more years are not required.

Finally, it is emphasized that the aim of this study was to evaluate the changes in HDI, MMR and U5MR from 1980 to 2010 in certain West and South Asian countries as well as the relationship between these indices.

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Mass gathering preparedness and response: cross-border collaboration and coordination between Iraq and neighbouring countries[1]

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Introduction

Mass gatherings are highly visible, unique events attended by a sufficient number of people to potentially strain the public health resources of a community, state or nation. Mass gatherings present complex planning and preparedness challenges for the public health infrastructure. Given the fact that mass gatherings have become increasingly international in attendance, natural, accidental and deliberate risks to health security have become increasingly important elements to address during the planning of health measures.

The World Health Organization (WHO) Eastern Mediterranean Region is host to some of the world's largest mass gatherings (1). Many countries in the Region organize annual mass gatherings of different sizes and natures, each with their own specific risks. Iraq hosts some of the largest Muharram and Arbaeen gatherings globally, which are attended by large cohorts of pilgrims especially from neighbouring countries (Bahrain, Islamic Republic of Iran, Jordan, Kuwait, Lebanon and Pakistan) (*1*). Hosting of mass gathering events provides a unique opportunity to strengthen implementation of the International Health Regulations (IHR) (2005) (*2*), considering that these are events with potential for international public health consequences, as well as opportunity to increase relevant national public health capacities required under the IHR (2005).

To address these issues, the WHO Regional Office for the Eastern Mediterranean (WHO/EMRO) organized a subregional meeting on mass gathering preparedness and response: cross-border collaboration and coordination between Iraq and its neighbouring countries, in Beirut, Lebanon, from 28 to 30 March 2019 (*3*). The meeting was attended by national IHR focal points, key officials responsible for mass gathering arrangements, and key officials representing points of entry, in addition to representatives from the WHO Collaborating Centre for Mass Gatherings Medicine in Saudi Arabia and international organizations. WHO staff from headquarters, regional and country offices also attended the meeting.

The objectives of the meeting were to:

- share country best practices on mass gathering preparedness;
- prioritize public health issues and associated challenges;
- identify mechanisms and modalities to scale up public health preparedness in the context of mass gatherings; and
- enhance collaboration and communication between Iraq and neighbouring countries in the context of mass gatherings.

Summary of discussions

Proper processes for hazard assessment in relation to mass gatherings were discussed. Most countries have not performed an overall national risk assessment for hosting mass gatherings, and none have performed a targeted risk assessment for a specific mass gathering. Risk assessment should be undertaken for all mass gatherings regardless of its size and the number of attendees.

There is a need to develop standard operating procedures and identify appropriate triggers on when to activate an emergency response plan during a mass gathering. Cross-country collaboration is as an area that requires improvement, and there is a need for memoranda of understanding to maintain such practices.

The potential for mass gatherings to have security-related incidents necessitates a strong and coordinated response. In the event of an incident, specialized chemical, biological, radiological and nuclear (CBRN) teams and security forces need to be leading and coordinating the investigation and response.

There is a need to set priorities and objectives when considering the breadth of surveillance information required for mass gatherings. Health surveillance is therefore an essential component of evidence-based decision-making practices, and diverse mechanisms should be employed to capture desired cohorts. Coordination of data and reporting lines among countries and the sharing of relevant epidemiological data, including case definitions, is an area for improvement. There is a need to enhance the Early Warning, Alert and Response System (EWARS) in addition to event-based surveillance in neighbouring countries before, during and post mass gathering events.

Risk communication is a major area for improvement in countries, especially when considering an all-hazard

[1] This report is extracted from the Summary report on the subregional meeting on mass gathering preparedness and response: cross-border collaboration and coordination between Iraq and neighbouring countries, Beirut, Lebanon, 28–30 March 2019 (http://applications.emro.who.int/docs/IC_Meet_Rep_2019_EN_23813.PDF?ua=1).

approach in light of a mass gathering. Mapping of communication partners with regards to mass gatherings should be undertaken, and standard operating procedures outlining communication with the general public during a crisis should be developed.

Points of entry (e.g. airports, seaports, road entry points, etc.) have a unique role during mass gatherings; however, gaps exist in their required IHR implementation including vector surveillance and control. Most pressingly there is a need to develop vaccination requirements for the host country, and to subsequently disseminate these requirements widely to all sending/bordering countries. Ensuring resources are available to perform compliance checks for vaccination is important.

Recommendations

- Reviewing national legislations to facilitate the scaling up of public health preparedness and response for mass gatherings.
- Developing standard operating procedures/triggers on how/when to activate an emergency response plan during mass gatherings.
- Planning and conducting simulation exercises to test preparedness capacities, and conducting training for relevant personnel for the management of CBRN events.
- Developing standard operating procedures on correct handling of forensic samples, and training personnel on how to collect, store and transport samples.
- Conducting assessments of hospital safety and the emergency care system, using WHO assessment tools.
- Ensuring that emergency response plans and standard operating procedures address mass casualty incidents.
- Establishing agreements between countries (such as memoranda of understanding) for information sharing during mass gatherings, including public health surveillance data.
- Establishing joint rapid response teams for investigation and response to public health events.
- Developing standard operating procedures for risk communication with the public during emergencies
- Supporting the development of country work plans for mass gathering preparedness and response, and their implementation.
- Support oversight mechanisms of research during mass gatherings.
- Organizing and supporting bilateral country meetings on mass gathering preparedness and response.
- Establishing a regional network and roster of experts (including national experts, WHO and relevant partners) for the management of CBRN events.
- Supporting the documentation of countries' experiences and sharing of results and lessons learned.
- Providing training support, including e-learning, on mass gathering preparedness.
- Developing an inventory of laboratory capacities and laboratory collaborating centres in the Region to share with countries.
- Developing advocacy materials highlighting the importance of scaling up public health preparedness for mass gatherings, targeting difference audiences including high-level officials.

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الدكتور عبد الرحمن العوضي (١٩٣٦–٢٠١٩)

تلقت أسرة منظمة الصحة العالمية ببالغ الأسى خبر وفاة الأستاذ الدكتور عبد الرحمن العوضي في ٦ يوليو/ تموز ٢٠١٩، بعد حياة حافلة بالعطاء والإنجازات، تاركاً أثراً طيباً يُذكَر به عبر تعاقب الأجيال.

وُلد الدكتور عبد الرحمن العوضي عام ١٩٣٦ في الكويت، وتخرج في كلية العلوم الصحية بالجامعة الأمريكية في بيروت عام ١٩٥٨. وحصل على الدكتوراه في الطب من جامعة أبردين عام ١٩٦٣، كما حصل على الماجستير في الصحة العامة من جامعة هارفارد بالولايات المتحدة الأمريكية عام ١٩٦٥. وتخصص في مجال الصحة العامة. وتدرج الدكتور العوضي في المناصب التي شغلها في وزارة الصحة الكويتية حتى عُيِّن وزيراً للصحة في ١٩٧٥ وشغل هذا المنصب حتى عام ١٩٨٦. وعمل على تطوير القطاع الصحي في الكويت وتعزيز الخدمات الصحية الوقائية والعلاجية لتواكب نظيراتها العالمية، وافتُتح في عهده عدد كبير من المستشفيات والمرافق الصحية. كما فاز بعضوية مجلس الأمة الكويتي عام ١٩٧٥، وشغل عدة مناصب مهمة في الدولة، حيث شغل منصب وزير التخطيط (١٩٨٤–١٩٨٦)؛ وعُين وزيراً للدولة لشؤون مجلس الوزراء (١٩٩٠–١٩٩١). وتقلد كثيرًا من المناصب في العديد من المحافل الوطنية والإقليمية والدولية. وحرص الدكتور العوضي على تعريب عدد كبير من الدراسات الطبية، كما أنجز أبحاثًا عديدة متعلقة بالبيئة.

ونال العديد من الدرجات الفخرية، أبرزها: الزمالة الفخرية للكلية الملكية للطب في أيرلندا عام ١٩٧٧؛ والكلية الملكية للجراحين والأطباء في جلاسكو – المملكة المتحدة في ١٩٨٢. كما فاز بكثير من الجوائز مثل جائزة مؤسسة الإمارات العربية المتحدة للصحة؛ وجائزة الشيخ حمدان بن راشد آل مكتوم للعلوم الطبية. كما كرمته اللجنة الإقليمية لمنظمة الصحة العالمية لشرق المتوسط عام ٢٠١٣ تقديراً لإسهاماته القيمة في مجال الصحة.

سيبقى الدكتور العوضي حاضراً في أذهان الأجيال المتعاقبة بشخصيته الطيبة وحضوره الذي يدفئ الفضاء حوله بالمودة الصادقة، ويزينه بالأمل والتفاؤل.

رحم الله الدكتور العوضي وأسكنه فسيح جناته

Professor Abdulrahman Al Awadi (1936–2019)

It is with deep sorrow that the World Health Organization learned of the passing away of Professor Abdulrahman Al Awadi on 6 July 2019, ending a life of great accomplishments and achievements.

Professor Abdul Rahman AI Awadi was born in 1963 in Kuwait. He graduated from the Faculty of Health Sciences, the American University in Beirut (1958). He obtained his Ph.D in medicine from Aberdeen University, United Kingdom (1963); and MA in Public Health from Harvard University, United States of America (1965). Professor Al Awadi specialized in public health and assumed different positions in the Ministry of Health until he was appointed as the Minister of Health from 1975 to 1986. During his tenure, the health sector in Kuwait witnessed a significant progress in the area of health services, with quality no less than international standards, and a large number of hospitals and health facilities were also established. He became a member of the National Assembly of Kuwait (1975) where he assumed different key State positions and was appointed Minister of Planning (1984–1986) and Minster of State for Cabinet Affairs (1990–1991). In addition, Professor Al Awadi served in many national, regional and international organizations, and also helped promote the arabization and translation of several medical studies as well as contributing to a number of research studies on the environment.

Professor Al Awadi was awarded various honorary degrees, including an Honorary Fellowship of the Royal College of Surgeons in Ireland (1977), and an Honorary Fellowship of the Royal College of Physicians and Surgeons of Glasgow, United Kingdom (1982). He also received many awards and prizes, such as the United Arab Emirates Annual Health Award, and the Sheikh Hamdan Bin Rashid Al Maktoum Award for Medical Sciences. He was also honoured by the World Health Organization Regional Committee for the Eastern Mediterranean for his valuable contributions to health (2013).

Professor Al Awadi will always be remembered by successive generations for his pleasant personality and presence, friendly manner and relentless optimism.

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