SUPPLEMENT 1

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Health and Medical Research Fund

Research Dissemination Reports

醫療衞生研究基金

研究成果報告

Alcohol control
酒精控制

Cancer
癌症

Healthcare technology
醫療技術

Infectious diseases
傳染病

Reproductive health
生殖健康

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Volume 29 Number 1 **February 2023**
SUPPLEMENT 1

Health and Medical Research Fund

Research Dissemination Reports

INFECTIOUS DISEASES

REPRODUCTIVE HEALTH

Editorial

Dissemination reports are concise informative reports of health-related research supported by the Health and Medical Research Fund administered by the Health Bureau. In this edition, we present 13 dissemination reports of projects related to alcohol control, cancer, healthcare technology, infectious diseases, and reproductive health. In particular, research findings of three projects may provide insights to enhance clinical practices and help inform health policy formulation in Hong Kong.

According to the World Health Organization, alcohol consumption is a causal factor in more than 200 diseases, injuries, and other health conditions.[1] The public health effort in raising awareness of the health and social problems caused by harmful use of alcohol is counterbalanced by positive images from alcohol industry marketing. Evidence-based interventions are required to reduce harmful drinking, especially in young people. Kim et al[2] aimed to determine the proportion of Hong Kong young adults who have been exposed to various types of social media marketing (SMM) and the associations between alcohol SMM exposure, alcohol expectancies, and drinking behaviours. They found that exposure to alcohol SMM was associated with all past-month drinking behaviours and future drinking intentions. Male, university-educated, and having lower monthly household income were more likely to be exposed to alcohol SMM. However, despite the widespread alcohol SMM, most young adults participating in the study considered that no restriction on alcohol SMM was necessary.

Hong Kong is rapidly transitioning to an ageing society and the pace of ageing has become faster in recent years, mainly due to post-war baby boomers entering old age. In 2020, the incidences of cancers climbed steadily as the population aged,[3] and cancer burden is expected to rise. Age-period-cohort models can be used to summarise information that is routinely collected by cancer registries and registries for other diseases. Using an age-period-cohort model, Wong et al[4] aimed to project the incidences of common cancers in Hong Kong, identify significant changes in cancer disease trends over time, and quantify the effect of demographic changes on future cancer incidences. They found that incidences of breast, endometrial, and thyroid cancers in women as well as incidences of colorectal and prostate cancer in men have increased over the past 30 years and are expected to continue to increase. Population growth and ageing have contributed to these increases in cancer incidences and are expected to continue to do so. Primary prevention by promoting healthier lifestyles and earlier cancer detection is recommended.

Chronic viral hepatitis is a risk factor for development of hepatocellular carcinoma (HCC). According to the Hong Kong Cancer Registry,[3] liver cancer (including neoplasm of liver and intrahepatic bile ducts) was the fifth most common cancer in Hong Kong in 2020. The Hong Kong Viral Hepatitis Action Plan 2020-2024 aims to reduce the burden of chronic viral hepatitis through effective prevention, treatment, and control of viral hepatitis. Many HCC risk prediction models are based on regression analysis. Machine-learning approaches that maximise data use and minimise bias are increasingly used for model development. Wong et al[5] aimed to develop prediction models using machine-learning algorithms to define the risk levels of HCC in patients with chronic viral hepatitis. They found that the machine-learning models generated accurate risk scores for HCC in patients with chronic viral hepatitis. The newly developed HCC ridge score was consistently more accurate in predicting HCC in chronic viral hepatitis patients than other commonly used methods. Such machine-learning methods may be useful for incorporating into electronic health systems to guide cancer surveillance strategies and reduce cancer death.

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Association of alcohol social media marketing with young adult drinking expectancies and behaviours: abridged secondary publication

JH Kim *, BHK Yip, RHW Chan

KEY MESSAGES

1. Exposure to alcohol social media marketing is associated with all past-month drinking behaviours and future drinking intentions.
2. Those who are male, university educated, and with lower monthly household income are more likely to be exposed to alcohol social media marketing.
3. Greater exposure to alcohol social media marketing is associated with higher positive drinking expectancies score.
4. Beliefs about positive outcomes of drinking mediate the association between exposure to alcohol social media marketing and drinking behaviours.
5. There is low public support for regulating digital alcohol marketing in this age group.

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Introduction

The negative health effects of excessive alcohol consumption are counterbalanced by positive images promulgated by alcohol industry marketing, particularly towards the youth. Exposure to alcohol advertising is associated with the uptake of drinking among the youth and development of brand allegiance.[1]

Social media disseminates user-generated content through posting, sharing, tagging, and liking content to their communities, thereby actively engaging the public to create and circulate content. Youth exposure to social media marketing (SMM) including direct business-to-consumer marketing (eg company Facebook pages) and consumer-to-consumer content (eg content sharing among friends) is associated with increased alcohol uptake. Such exposure highly influences expectancy, which is the perceived positive and negative outcomes of a certain behaviour. Alcohol-related expectancies are strongly associated with consumption levels and problem drinking among youths.[2]

Since 2008 in Hong Kong, elimination of wine and beer duties has resulted in increased promotion of alcohol products.[3] To reduce harmful drinking in young people, evidence-based interventions are needed. This study aims to determine the proportion of Hong Kong young adults who have been exposed to various types of alcohol SMM, the prevalence and types of their engagement in alcohol SMM, and the associations between alcohol SMM exposure and alcohol expectancies and drinking behaviours.

Methods

From June to August 2021, a telephone survey was conducted for 675 Chinese residents of Hong Kong aged 18 to 34 years by trained interviewers. The questionnaire collected respondents' socio-demographic and background data, exposure to traditional marketing and SSM for alcohol, past-month drinking behaviour and future drinking intention, alcohol-related expectancies, and attitudes around regulations.

The level of exposure to alcohol SMM was quantified by summing the past-month exposure to various alcohol SMM. Exposure above the interquartile range were classified as higher exposure. Backward elimination multivariable logistic regression analysis was conducted to identify factors associated with past-month-drinking behaviours and future drinking intentions as well as drinking expectancies scores. The PROCESS macro (version 4.0) was used for mediation influence tests for non-continuous outcome variables.[4]

Results

A total of 334 men and 341 women were included. The sample was representative of the Hong Kong Census population of the same age group,[5] except that our sample had a higher proportion of university-educated individuals (51.9% vs 46.1%) and a lower proportion of employed individuals (69.2% vs 74.8%). The prevalence of lifetime drinker, past-year drinker, past-month binge drinker, and problem drinker (based on the CAGE questionnaire) was 80.1%, 53%,

12.4%, and 3.9%, respectively. More young adults were exposed to traditional marketing than SMM in the past month (71.6% vs 53%, P<0.001).

53% of respondents had been exposed to any alcohol SMM, with direct business-to-consumer SMM more than indirect consumer-to-consumer SMM (40.9% vs 32.1%). Those who were male, aged 25 to 29 years, university educated, and with lower household income were more likely to have been exposed to past-month alcohol SMM (Table 1).

Higher past-month exposure to alcohol SMM was associated with all drinking behaviours and future drinking intentions even after adjusting for confounding factors (Table 2). By contrast, exposure to traditional alcohol marketing was associated with past-month drinking and future intention to drink only. Higher educational attainment was associated with past-month drinking, past-month binge drinking, and future intention to drink. Those who were employed were less likely to binge drink or experience problem drinking, whereas those with a lower monthly household income were more likely to report problem drinking. Age was associated with weekly drinking only. Sex and marital status were not independent predictors for any drinking-related variables.

After adjusting for confounding factors, higher exposure to alcohol SMM was associated with a higher Chinese Drinking Expectancy Questionnaire (CDEQ) positive drinking expectancies score (Table 3). Higher exposure to alcohol SMM was independent predictor for higher scores of the Interpersonal Benefits, Increased Confidence, and Tension Reduction subscales of the CDEQ. CDEQ score of positive drinking expectancies was associated with mediation effects on all drinking behaviours except for future intention to get drunk. Similarly, the Interpersonal Benefits and Tension Reduction subscale scores mediated the effect of high exposure to alcohol SMM on past-month drinking (12.8% and 116.5%, respectively), weekly drinking (19.6% and 17.1%, respectively), binge drinking (8.5% and 8.15%, respectively), problematic drinking (7.0% and 9.5%, respectively), and future intention to drink (4.5% and 3.6%, respectively) but not future intention to get drunk. Increased confidence subscale score

TABLE 1. Association of past-month exposure to alcohol social media marketing (SMM) with sociodemographic factors (n=675)

Variable	All SMM			Direct SMM			Indirect SMM		
	Exposure, %	P value	Adjusted odds ratio (95% confidence interval)	Exposure, %	P value	Adjusted odds ratio (95% confidence interval)	Exposure, %	P value	Adjusted odds ratio (95% confidence interval)
All (n=675)	53.0	-	-	40.9	-	-	32.1	-	-
Sex		0.001			<0.001			0.217	
Female (n=341)	46.6		1.00	33.4		1.00	29.9		-
Male (n=334)	59.6		1.73 (1.25-2.40)†	48.5		1.84 (1.32-2.58)‡	34.4		-
Age, y		0.007			0.004			0.007	
30-34 (n=256)	45.3		1.00	32.8		1.00	25.4		1.00
25-29 (n=200)	57.5		1.57 (1.05-2.36)*	45.0		1.33 (0.88-2.03)	33.5		1.65 (1.07-2.52)*
18-24 (n=219)	58.0		1.31 (0.88-1.95)	46.6		1.29 (0.85-1.94)	38.8		1.82 (1.21-2.74)†
Education level		0.002			<0.001			0.805	
Below university	46.8		1.00	26.5		1.00	32.6		-
University or higher	58.9		2.26 (1.59-3.21)‡	54.3		3.78 (2.64-5.43)‡	31.7		-
Marital status		0.169			0.011			0.854	
Married/other	48.7		1.00	33.2		1.00	31.6		-
Single	54.7		0.95 (0.61-1.46)	43.9		1.11 (0.71-1.74)	32.4		-
Employment		0.677			0.398			0.004	
Non-employed	54.3		-	38.5		-	39.9		1.00
Employed	52.5		-	42.0		-	28.7		0.87 (0.56-1.35)
Monthly household income, HK$		<0.001			0.201			<0.001	
≥40 000	44.4		1.00	39.7		1.00	23.8		1.00
<40 000	62.8		2.81 (1.98-3.98)	44.9		1.89 (1.32-2.70)‡	40.3		2.13 (1.51-2.99)‡

* P<0.05
† P<0.01
‡ P<0.001

TABLE 2. Association of past-month exposure to alcohol social media marketing (SMM) with past drinking behaviour and future drinking intention (n=675)

Variable	Adjusted odds ratio (95% confidence interval)					
	Past month drinking	Weekly drinking	Past-month binge drinking	Problematic drinking (based on the CAGE questionnaire)	Future intention to drink	Future intention to get drunk
Higher levels of past-month exposure to alcohol SMM (vs lower)	1.93 (1.28-2.90)‡	2.63 (1.16-5.95)†	3.84 (2.37-6.23)§	3.49 (1.46-8.39)‡	4.85 (3.09-7.61)§	7.85 (1.68-36.6)‡
Exposure to traditional media marketing (vs none)	2.13 (1.21-3.74)‡	3.35 (0.73-15.4)	-	1.63 (0.49-5.38)	2.21 (1.13-4.32)†	-
Sex						
Female	1.00	-	1.00	-	1.00	-
Male	1.37 (0.92-2.03)	-	1.24 (0.76-2.02)	-	1.31 (0.86-1.99)	-
Age, y						
30-34	1.00	-	1.00	1.00	1.00	-
25-29	2.56 (1.56-4.19)§	-	1.81 (0.97-3.38)*	0.22 (0.05-1.08)*	1.43 (0.82-2.49)	-
18-24	1.29 (0.78-2.18)	-	0.95 (0.48-1.90)	0.82 (0.29-2.25)	0.97 (0.55-1.74)	-
Education level						
Below university	1.00	-	1.00	-	1.00	1.00
University or higher	2.02 (1.33-3.06)‡	-	1.61 (0.95-2.74)*	-	2.15 (1.37-3.38)‡	1.98 (0.48-8.09)
Marital status						
Married/cohabiting	-	-	-	-	1.00	-
Single	-	-	-	-	1.22 (0.73-2.04)	-
Employment						
Non-employed	-	-	1.00	1.00	-	-
Employed	-	-	0.57 (0.35-0.93)†	0.33 (0.14-0.78)†	-	-
Monthly household income, HK$						
≥40 000	-	1.00	-	1.00	-	1.00
<40 000	-	2.14 (0.86-5.29)	-	8.36 (1.91-36.59)‡	-	2.32 (0.60-8.89)

* P<0.10
† P<0.05
‡ P<0.01
§ P<0.001

only mediated the effect of past-month exposure to alcohol SMM on binge drinking (8.15%) and problem drinking (16.4%).

Only 14.2% of respondents supported greater government restriction on alcohol SMM, whereas 85.3% reported no need for change. Among those supported for greater restriction for alcohol SMM, only being a binge drinker (adjusted odds ratio [AOR]=2.25, 95% confidence interval [CI]=1.25-4.04) and having a lower monthly household income (AOR=2.27, 95% CI=1.42-3.62) were independent predictors for supporting greater restriction for alcohol SMM.

Discussion

Higher alcohol SMM exposure was associated with various positive drinking expectancies, past drinking behaviours, and future drinking intentions. Positive drinking expectancies could mediate the effect of alcohol SMM on various drinking behaviours.

Young adults who were male, university-educated, aged 25 to 29 years, with lower household income were more likely to be exposed to alcohol SMM and thereby represent the target groups for public health actions. Higher exposure to alcohol SMM was associated with all drinking behaviours. Mediation analyses performed with each of the CDEQ subscales showed that the Interpersonal Benefits, Increased Confidence, and Tension Reduction subscales mediated the effect of past-month SMM exposure on drinking behaviours. Alcohol SMM often invoke themes of relaxation and collegiality. The findings thereby provide an evidence-based intervention to counterbalance alcohol SMM by public health workers.

TABLE 3. Mediation analysis model of exposure to alcohol social media marketing (SMM) with total Chinese Drinking Expectancy Questionnaire (CDEQ) score as mediator

Drinking outcome	Higher exposure to alcohol SMM on CDEQ score (x on mediator)	Total CDEQ score on drinking outcome (mediator on y)	Higher exposure to alcohol SMM on outcome (x on y)	Indirect effect (m-x on y)	% mediation by total CDEQ expectancies (indirect effect/total effect)
	Estimated regression coefficient (standard error)			Indirect effect (standard error) [95% confidence interval]	
Past month drinking	1.41 (1.06)	0.01 (0.01)	0.99 (0.19)§	0.01 (0.02) [-0.01-0.05]	-
Weekly drinking	1.41 (1.06)	0.04 (0.02)‡	0.89 (0.42)†	0.06 (0.61) [-0.03-0.2]	-
Binge drinking	1.41 (1.06)	0.02 (0.01)†	1.32 (0.25)§	0.03 (0.03) [-0.01-0.11]	-
Problematic drinking	1.41 (1.06)	0.06 (0.02)§	1.29 (0.44)‡	0.09 (0.08) [-0.05-0.27]	-
Future intention to drink	1.41 (1.06)	-0.01 (0.01)	1.95 (0.22)§	-0.01 (0.01) [-0.03-0.03]	-
Future intention to get drunk	1.41 (1.06)	-0.02 (0.02)	2.08 (0.79)‡	-0.03 (0.06) [-0.14-0.11]	-
	Higher exposure to alcohol SMM on CDEQ positive score (x on mediator)	CDEQ positive score on drinking outcome (mediator on y)	Higher exposure to alcohol SMM on outcome (x on y)	Indirect effect (m-x on y)	% mediation by CDEQ positive expectancies (indirect effect/total effect)
Past month drinking	2.47 (0.87)‡	0.04 (0.01)§	0.92 (0.19)§	0.11 (0.05) [0.03-0.22]	10.8%
Weekly drinking	2.47 (0.87)‡	0.07 (0.02)§	0.78 (0.42)*	0.18 (0.09) [0.03-0.39]	18.9%
Binge drinking	2.47 (0.87)‡	0.06 (0.01)§	1.24 (0.25)§	0.14 (0.07) [0.03-0.30]	10.1%
Problematic drinking	2.47 (0.87)‡	0.08 (0.02)§	1.21 (0.44)‡	0.19 (0.10) [0.04-0.43]	13.5%
Future intention to drink	2.47 (0.87)‡	0.03 (0.01)‡	1.90 (0.22)§	0.08 (0.04) [0.01-0.18]	4.05%
Future intention to get drunk	2.47 (0.87)‡	-0.02 (0.03)	2.11 (0.79)‡	-0.06 (0.11) [-0.26-0.20]	-

* P<0.10
† P<0.05
‡ P<0.01
§ P<0.001

Despite the widespread alcohol SMM, most young adults believed that no restriction is needed. SSM is less intrusive, and recipients may not identify SSM as marketing. The lack of support for regulation may reflect scepticism about the effectiveness and feasibility of regulating SMM in Hong Kong. Nonetheless, the greater support among binge drinkers suggests that increasing public awareness of the adverse effects of drinking may help to increase public support for stronger regulations.

The main limitation of this study was the mandatory closure of bars/nightclubs during the COVID-19 pandemic. The drinking behaviours may not have been typical of Hong Kong young adults during the pandemic. We delayed the data collection until venues were allowed to open. In addition, the cross-sectional data cannot ascertain the temporal sequence of associations. Future research should record longitudinal changes in drinking behaviours in relation to alcohol SMM and examine the content of alcohol SMM advertisements and promotional strategies to inform policy makers.

Funding

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Disclosure

The results of this research have been previously published in:

1. Chan RHW, Dong D, Kim JH. Drinking expectancies among Chinese young adults: a qualitative study from Hong Kong. Int J Environ Res Public Health 2022;19:11865.

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Epidemiological and demographic contributions to future cancer burden in Hong Kong: abridged secondary publication

IOL Wong *, BJ Cowling, YT Lam, KF Lam

KEY MESSAGES

1. Incidences of breast, endometrial, and thyroid cancers in women as well as incidences of colorectal and prostate cancers in men have increased in the last three decades and are expected to continue to increase.
2. Population growth and population ageing have contributed to the increase in cancer incidences and are expected to continue to do so.
3. Increases in resources and collaboration between disciplines and healthcare sectors are necessary to enhance surveillance and monitoring of cancer disease trends.

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Introduction

In Hong Kong, the top five cancers for men are lung, prostate, colorectal, stomach, and liver cancers, and for women are breast, colorectal, lung, cervix uteri, and thyroid cancers. There is an increasing trend in incidences of breast, endometrial, and thyroid cancers in women and colorectal and prostate cancers in men.[1] Hong Kong is in a rapid transition to an ageing society. Cancer is predominately a disease of older people; >50% of patients were diagnosed with cancer after the age of 60 years in Hong Kong.[2] Cancer disease burden is expected to increase in the ageing population. This study aims to project the incidence of cancers in Hong Kong using the age-period-cohort model, identify significant changes in cancer disease trends over time, and quantify the effect of demographic changes on future cancer incidence.

Methods

Data of age-specific cancer incidences of top five cancers in men and in women in 2017 were retrieved, based on the International Classification of Diseases Tenth Revision codes of C33-34, C18-21, C61, C22, C16, C50, C54, and C73.

The age-period-cohort Poisson regression model was used to decompose the temporal trends of cancer incidences into three components of time, namely the effects of chronological age on incidence, birth cohort/generation, and calendar time period of incidence. An updated projection approach was used based on past observations and prior knowledge to predict age-specific incidences of selected cancers in men and in women in Hong Kong in short and medium term.

To analyse the trends in incidences, joinpoint regression[3] was used to break down the overall trend into several linear trends over the periods and to identify the breakpoints (ie, inflection points). The annual percentage changes (APCs) in each period were calculated, as were the overall average annual percentage changes (AAPCs).

The RiskDiff method was used to apportion the temporal variations in observed incidences of cancers into three components: population size, population structure, and cancer risk.[4] Populations in an earlier period and in a later period were standardised to equal sizes and then age-specific incidence rates were applied in the earlier period to the population structure in the later period.[4] The RiskDiff method enables decomposition of changes in the number of cases secondary to changes in population structure and cancer risk, leaving changes in population size as the remaining component.[4]

Results

Overall, the trends of age-standardised incidence rates from 1983 to 2017 were downwards in both men (AAPC= -1.08) and women (AAPC= -0.20). For individual cancers, the trends of age-standardised incidence rates for lung cancer in women and of liver, lung, and stomach cancers in men were downwards, whereas the trends for breast, endometrial, and thyroid cancers in women and for colorectal and prostate cancers in men were upwards (Fig 1).

In the age-period-cohort Poisson models, incidences for colorectal and prostate cancer in men and for breast, endometrial, and thyroid

cancers in women were projected to continue to increase, whereas incidences for liver, lung, and stomach cancers in men were projected to continue to decrease, and incidences for colorectal and lung cancers in women were projected to remain stationary. Age-standardised incidence rates for lung cancer decreased more markedly for men than for women (Fig 2).

Generally, incidence of cancers increased steadily as age increased until late middle age, with downward inflection at older old ages (85 years). Incidences of breast, colorectum, and lung cancers in women and of colorectum, lung, and prostate cancers in men increased more rapidly with age. The effects of birth cohort were strong on breast, endometrial, and thyroid cancers in women and prostate cancer in men. Period effects were also observed in these cancers.

The trends in the number of new cases of individual cancers have increased from 1983 to 2017, except for liver and stomach cancers in men, which plateaued. Changes attributed to population structure and population size were all positive and corresponded to population ageing and population growth. Changes attributed to cancer risk were negative for colorectal and lung cancers in women and lung, liver, stomach cancers in men, whereas changes attributed to cancer risk were positive for breast, endometrial, and thyroid in women and colorectal and prostate cancers in men (Fig 3).

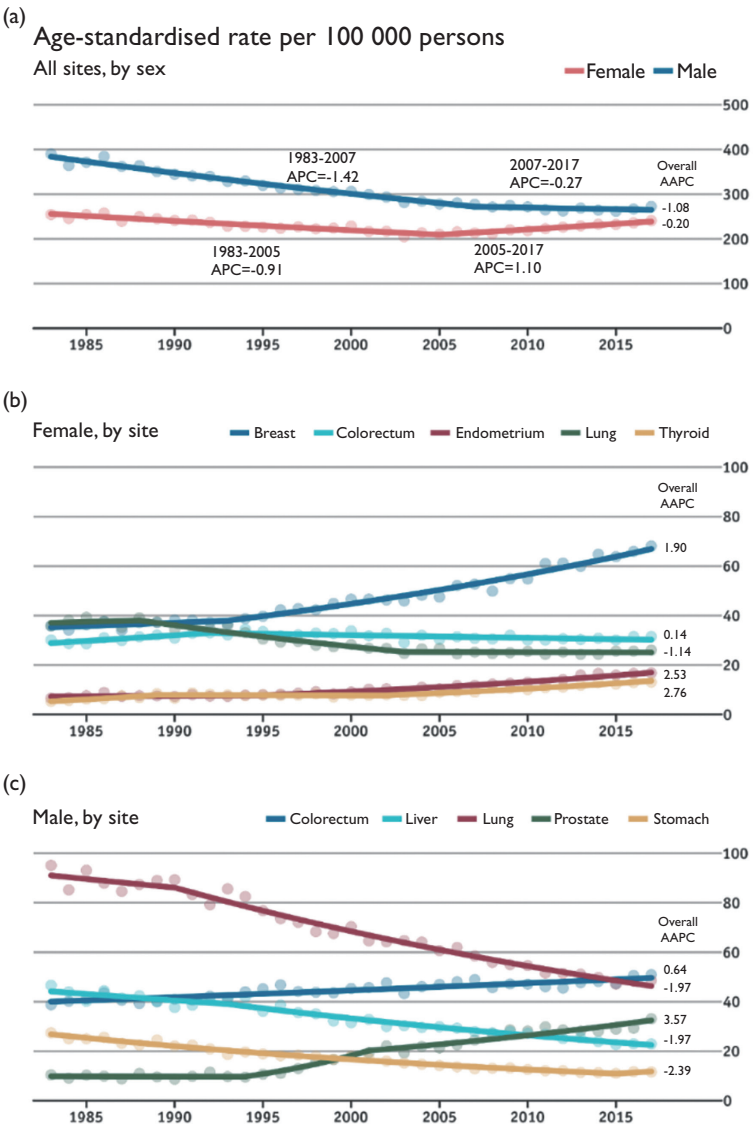

FIG 1. Annual age-standardised incidence rates of (a) all cancers combined, (b) top five cancers for women, and (c) top five cancers for men in Hong Kong from 1983 to 2017, as well as the average annual percentage change (AAPC) and annual percentage change (APC)

Discussion

In the past three decades in Hong Kong, age-standardised incidence rates of all cancers have decreased, but the overall number of cases increased dramatically, primarily driven by ageing and cohort/generation effects, particularly for breast, endometrial, and thyroid cancers in women and prostate cancer in men, which were also attributed by period effects. Incidences of breast, endometrial, and thyroid cancers in women and prostate cancer in men were projected to continue to increase. Compared with 2013 to 2017, by 2028 to 2032, the increase in the number of cases was expected to be 83.0%, 119.0%, 85.0%, and 127.1% for breast, endometrial, thyroid cancers in women and prostate cancer in men, respectively. The increase in prostate cancer in men was expected to be mostly due to population ageing and increased cancer risk, whereas the increase in breast, endometrial, and thyroid cancers in women was expected to be mostly due to increased cancer risk, although population ageing and population growth also contributed considerably (Fig 3). Thus, cancer screening and healthier lifestyle promotion are recommended to mitigate cancer risk.

Birth cohort/generation and period effects were strong on breast, endometrial, and thyroid cancers in women and prostate cancer in men. Epidemiological transitions (receding of infectious diseases and emergence of degenerative conditions secondary to improvement in public health and sanitation) might be an explanation to changes in disease patterns or cancer risks of populations.[5] More dominant period effects were observed for hormonally modulated cancers including breast, endometrial, and thyroid cancers in women and prostate cancer in men. We speculate that these changes in period effects may be accounted for by better cancer detection and diagnosis strategies in recent years.

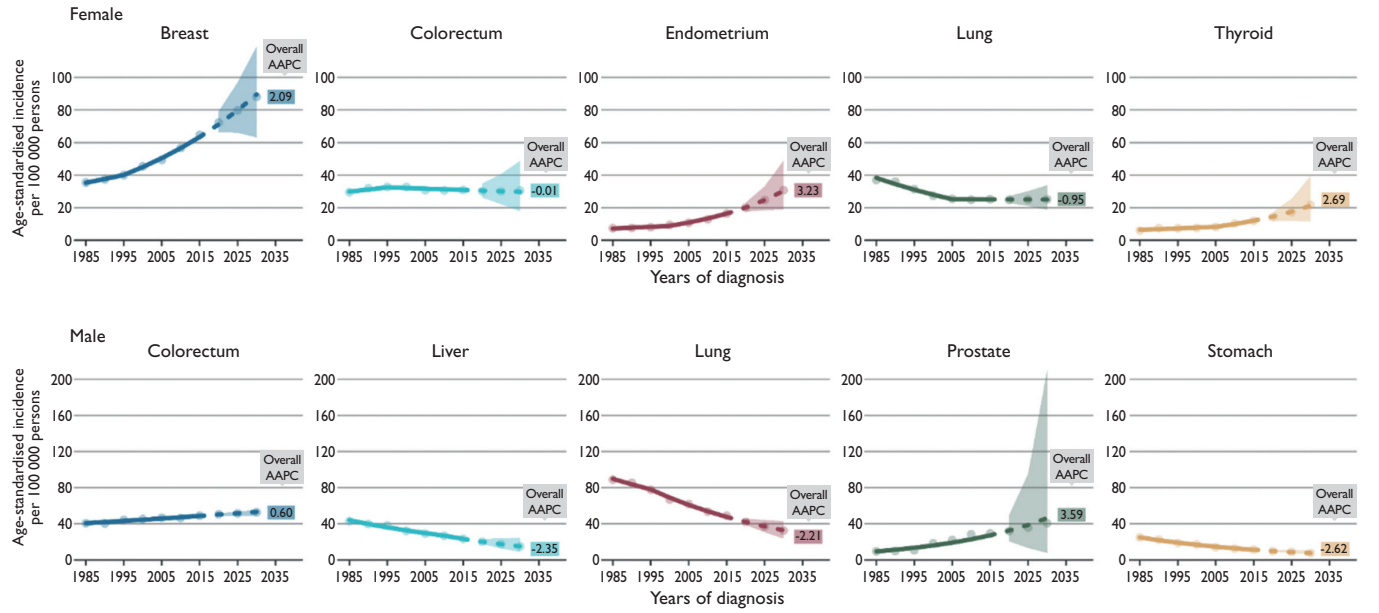

FIG 2. Age-standardised incidence rates and overall average annual percentage change (AAPC) of the top five cancers in women and in men in Hong Kong from 1983 to 2017, as well as projected incidence rates in 2018-2022, 2023-2027, and 2028-2032 with 95% credible intervals

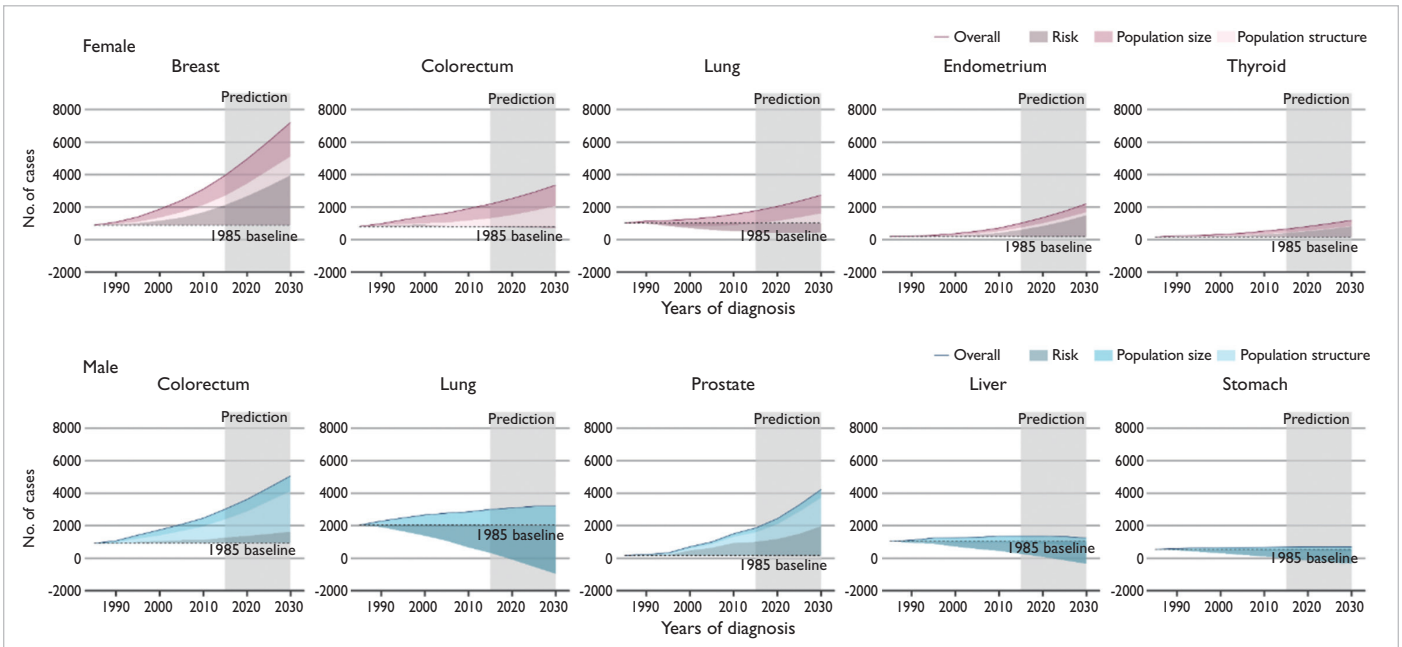

FIG 3. Trends in number of new cases for top five cancers attributed to changes in cancer risks and diagnostic practices (ie, epidemiological components), population size and structure (ie, demographic components) for women and men in Hong Kong from 1983 to 2017

Increases in numbers of cases were mostly attributable to population growth and population ageing in overall and individual cancers in both sexes (Fig 3). Cancer burden change was mostly associated with population ageing and population growth, whereas the variation in the temporal pattern of the cancer risk was likely to be associated with extended cancer screening and epidemiological transition. We therefore recommend primary prevention and early cancer detection to combat the trend.

Conclusions

Population growth and ageing in Hong Kong

resulted in a marked increase in the number of cancer cases in the past decades, whereas the overall age-standardised incidence rates of cancers have decreased in the same period. The numbers of cancer cases are projected to continue to increase from 2018 to 2032. Thus, primary prevention by promoting healthier lifestyles and earlier cancer detection is recommended. The surge in overall numbers of cases is expected to stress out our healthcare system. More study is warranted for the cohort/generational effects on breast, endometrial, and thyroid cancers in women and prostate cancer in men. We recommend increase in resources and collaboration between disciplines and healthcare sectors to enhance surveillance and monitoring of cancer disease trends. We also need to adjust our cancer treatment care and surveillance in view of increasing demand from older people.

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Disclosure

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Targeting androgen receptor in BQ323636.1 overexpressing oestrogen receptor-positive breast cancer to overcome aromatase inhibitor resistance: abridged secondary publication

H Tsoi, EPS Man, J Lok, CN Cheng, LS Wong, SY Chan, MH Leung, WL Chan, US Khoo *

KEY MESSAGES

1. BQ323636.1 overexpression enhances the activity of androgen receptor (AR) signalling and reverses the tumour suppressive effect of aromatase inhibitors (AI).
2. High nuclear BQ323636.1 (BQ) and AR expression is associated with AI resistance and poorer survival in post-menopausal oestrogen receptor-positive (ER+) breast cancer patients.
3. Co-treatment with AR inhibitor, bicalutamide can recover the therapeutic effect of AI in ER+/BQ+/AR+ breast cancer.

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Introduction

Breast cancer can be classified into hormonal receptor-positive, HER2 overexpressed, and triple-negative breast cancer subtypes, and treatment for each subtype differs entirely. Most oestrogen receptor-positive (ER+) tumours initially depend on ER-activation by the steroid hormone oestrogen. Oestrogen-induced ER activation promotes proliferation and survival of breast tissue through transcription of pro-survival genes (genomic regulation) and activation of cellular signalling (non-genomic regulation).[1] Activated ER can promote cell proliferation, leading to cancer development. Oestrogen suppression remains the mainstay of ER+ breast cancer treatment.

Adjuvant endocrine therapy is recommended for patients with ER+ breast cancer to prevent metastasis and local recurrence. The aromatase inhibitors (AI) such as anastrozole, letrozole, and exemestane are options for post-menopausal patients. We previously identified a novel splice variant of NCOR2 and BQ323636.1 (BQ), which present in most primary breast cancers and associated with tamoxifen resistance.[1] NCOR2 is a nuclear receptor co-repressor that suppresses transcription through interaction with transcription factors. ER-α and androgen receptor (AR) are targets of NCOR2.[2] Although NCOR2 can repress the activities of ER and AR, BQ overexpression abolishes the repressive role of NCOR2 by forming a BQ-NCOR2 functionless dimer, leading to ligand-independent activation of ER.[3] High nuclear BQ expression is associated with tamoxifen resistance.[3] We proposed that BQ might use a similar mechanism to enhance the activity of AR in breast tumours. Hijacking AR signalling is the driving factor of prostate cancer. AI inhibits the conversion of androgen to oestrogen to repress ER signalling. Thus, AI treatment can lead to more androgen being available for enhanced AR activity. This increased availability of androgen together with enhanced AR activity in BQ-overexpressing cells might lead to over-activation of AR signalling, which could have an oncogenic effect. We hypothesise that AR over-activation in BQ-overexpressing cells can interfere with the tumour suppressive effect of AI. This study illustrates that supressing AR can recover the therapeutic value of AI in ER+/AR+/BQ+ breast cancer.

Inhibition of AR signalling to recover tumour suppressive effect of AI in ER+/BQ+/AR+ breast cancer in vitro and in vivo

After the maximum non-lethal dosage of the AR antagonist—bicalutamide (BIC)—was determined, cell viability assay showed that co-treatment with AI and BIC in BQ-overexpressing cells (MCF-7-BQ and ZR-75-BQ) resulted in reversal of the effect of AI treatment alone. Moreover, luciferase reporter assay showed that the addition of BIC abolished the effect of AI on ARE-activity. Cell cycle analysis via flow cytometry suggested that the addition of BIC could recover the cell cycle inhibition effect of AI. Western blot analysis confirmed this notion by detection of CDK2, CDK4, and CCNE1. These

results demonstrated that applying BIC on BQ-overexpressing cells could recover the tumour suppressive effect of AI.

To evaluate the effect of AR inhibition on recovering AI's efficacy in BQ-overexpressing tumours, ZR-75 and ZR-75-BQ cells transfected with CYP19A1 were implanted onto the mammary fat pad of ovariectomised nude mice. Treatment of 10 mg/kg of Arimidex, clinically used AI for menopausal ER+ breast cancer patients, could significantly suppress tumour development in ZR-75 xenograft. Similarly, AI alone enhanced tumour development in BQ overexpressed xenograft ZR-75-BQ; this effect was reversed by co-treatment with AR antagonist Casodex, the clinical equivalent of bicalutamide.

Clinical significance of BQ and AR in post-menopause ER+ breast cancer

In patients who had been treated with AI for at least 5 years, the expression of BQ and AR of 267 primary breast carcinomas in tissue microarray was examined by immunohistochemistry. High expression of BQ and AR was associated with AI resistance.

Kaplan-Meier survival analysis showed that patients with high BQ expression had poorer overall survival, disease-specific survival, and disease-free survival. Therefore, high nuclear BQ could be an indicator of poorer prognosis in ER+ post-menopausal patients with breast cancer who received AI adjuvant therapy. When combined expression of both BQ and AR was used, patients with both high BQ and AR expression also showed poorer overall survival, disease-specific survival, and disease-free survival, with greater discrimination in the combined analysis with survival curves further apart.

Discussion

Endocrine therapies such as selective ER modulators, selective ER down regulators, and AIs are used for adjuvant treatment of ER+ breast cancer. AI depletes systemic oestrogen in post-menopausal patients by blocking the conversion of androgens to oestrogens. AI therapy results in a more significant reduction in the risk of recurrence than 5-year tamoxifen therapy such that most post-menopausal women should consider AI treatment either as initial therapy or after 2 to 3 years of tamoxifen therapy. However, the occurrence of resistance is an obstacle.

Our study found that BQ overexpression in primary cancer could change the therapeutic effect of AI into a tumour-promoting agent. AI suppresses the activity of aromatase to convert androgen to oestrogen and thus suppress ER-signalling in ER+ breast cancer. However, the unconverted androgen might activate AR-signalling in the presence of AR. Luciferase reporter assay confirmed that BQ-overexpression could amplify AR-signalling intensity when AI was used. BQ is a splice variant of NCOR2.[1] NCOR2, being a co-repressor, forms a repressor complex to suppress transcription mediated by different transcription factors such as ER and AR.[2] BQ overexpression reduces the suppression of ER-signalling, resulting in tamoxifen resistance.[3] Likewise, it could also reduce the suppression of AR-signalling. AI treatment aims at eliminating the conversion of androgen. As a result, in terms of BQ overexpression, AI would work together to enhance the activity of AR signalling. AR expression is detected in about 60% to 90% of ER+ breast cancer. Thus, enhanced AR-signalling mediated by AI in BQ overexpressing breast cancer becomes a tumour driving factor. Suppression of AR signalling should reverse such an effect.

In patients with high BQ and AR expression, AI treatment was ineffective and even tumour-promoting. The use of an AR antagonist could reverse this effect. These findings are confirmed in primary breast cancer mouse models. High expressions of BQ and AR in ER+ patients treated with AI were associated with AI resistance and poorer survival outcomes. Therefore, we recommend examining the nuclear expression of AR and BQ in the primary breast cancer by immunohistochemistry.

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Disclosure

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1. You CP, Leung MH, Tsang WC, Khoo US, Tsoi H. Androgen receptor as an emerging feasible biomarker for breast cancer. Biomolecules 2022;12:72.
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Machine learning in predicting hepatocellular carcinoma in patients with chronic viral hepatitis in Hong Kong: abridged secondary publication

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KEY MESSAGES

1. Novel machine-learning models generate accurate risk scores for hepatocellular carcinoma (HCC) in patients with chronic viral hepatitis.
2. HCC ridge score is consistently more accurate than existing HCC risk scores.
3. These machine-learning models may be incorporated into electronic health systems to guide cancer surveillance strategies and reduce cancer death.

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Introduction

The Hong Kong Viral Hepatitis Action Plan 2020-2024 aims to reduce the burden of chronic viral hepatitis (CVH) through effective prevention, treatment, and control of viral hepatitis. A comprehensive review of the disease burden of CVH and accurate prediction of hepatocellular carcinoma (HCC) may help guide strategies and action plans and ultimately eliminate viral hepatitis. Most HCC risk prediction models are developed using regression analysis.[1,2] Machine learning is a comprehensive tool for model development.[3,4] It enables direct selection of predicting parameters without subjective preselection, maximising data use while minimising bias. This study aims to develop prediction models using machine-learning algorithms to define the risk levels of HCC in patients with CVH. These models can be incorporated into electronic health systems to facilitate clinical assessment and risk stratification of HCC in patients with CVH.

Methods

This territory-wide registry cohort study was conducted using data from the Hospital Authority Data Collaboration Laboratory, which provides anonymised and de-identified data from all public hospitals and clinics in Hong Kong, including demographics, inpatient admissions, transfers and discharges, outpatient appointments, diagnosis, procedures, medications, laboratory tests and results, radiology examinations, clinical notes and summaries, and radiology reports and radiology images.

Data of patients with CVH (chronic hepatitis B [CHB] and chronic hepatitis C [CHC]) between 1 January 2000 and 31 December 2018 were retrieved. CHB/CHC was defined by positive hepatitis B/C surface antigen for ≥6 months, and/or by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, and/or by use of antiviral treatment for CHB/CHC.

Baseline date was defined as the date of first diagnosis of CHB or CHC by viral markers, ICD-9-CM codes, or antiviral drugs, whichever came first. Liver biochemistries and haematological and virological parameters were collected. Antiviral treatment included oral nucleos(t)ide analogues for CHB as well as (pegylated)-interferon with or without ribavirin and direct-acting antivirals for CHC. Medication use was defined as those prescribed for ≥4 weeks. The severity of liver fibrosis was assessed with serum formulae, namely the aspartate transaminase to platelet ratio index, Fibrosis-4 index, and Forns index. Advanced liver fibrosis was defined as the aspartate transaminase to platelet ratio index of ≥2, Fibrosis-4 index of ≥3.25, or Forns index of ≥8.4.

Patients with HCC were identified by diagnosis codes (155.0 for hepatocellular carcinoma and 155.2 for carcinoma of liver) or procedure codes for HCC treatment. The use of single ICD-9-CM codes for diagnosis was 99% accurate when referenced to clinical, laboratory, imaging, and endoscopy results from electronic medical records.

Data were analysed using SPSS (Windows version 25; IBM Corp, Armonk [NY], US), SAS (9.4; SAS Institute, Cary [NC], US), and R software (3.5.1; R Foundation for Statistical Computing, Vienna, Austria). The cohort was randomly split into training and validation cohorts in a 7:3 ratio. Additional external validation was performed in an independent cohort of Korean patients. Five popular machine-

learning models (logistic regression, ridge regression, AdaBoost, decision tree, and random forest) were compared to determine the best prediction model. Accuracy of the models was assessed by the area under the receiver operating characteristic curve (AUROC). Dual cutoffs were selected to achieve 90% sensitivity and 90% specificity to rule out and rule in patients with HCC, while maximising the corresponding specificity and sensitivity, respectively. The model with the highest AUROC in the validation cohort was considered the most predictive model, which was compared with other HCC risk scores: CU-HCC (Chinese University-HCC), GAG-HCC (guide with age, gender, hepatitis B virus DNA, central promoter mutations and cirrhosis-HCC), REACH-B (risk estimate for hepatocellular carcinoma in chronic hepatitis B), PAGE-B (platelets, age, gender, and hepatitis B virus), and REAL-B (real-world effectiveness from the Asia Pacific rim liver consortium for hepatitis B virus). All tests were two-sided. A P value of <0.05 was considered statistically significant. P values for pairwise comparison were adjusted by Bonferroni correction.

Results

Of 266 017 patients with viral hepatitis identified, 117 640 were excluded and 148 377 with CVH (CHB=126 890, CHC=16 811, and both=4676) were included in analysis. The cohorts were predominantly male, and most patients had compensated liver disease. The prevalence of comorbidities generally increased over time.

51 572 (>40%) patients with CHB had received antiviral treatment by 2018. The cumulative treatment uptake increased from 12.05% during 2005-2009 to 17.76% during 2010-2013 to 40.64% during 2014-2018. Of them, 99.3% received nucleos(t)ide analogues and 1.9% received conventional or pegylated interferon. 5660 (>30%) patients with CHC had received antiviral treatment by 2018. Of them, 92.2% received conventional or pegylated interferon and ribavirin and 7.8% received direct-acting antivirals, which became available in Hong Kong in late 2013.

A total of 124 006 patients were included in developing machine-learning models to predict HCC, with inclusion of all 46 parameters at baseline, in which 36 or 20 selected parameters had best predictive power (Table 1). In the training cohort (n=86 804, HCC=6821), random forest, decision tree, and ridge regression performed the best with inclusion of all 46 parameters (AUROC=0.992, 0.800, and 0.842, respectively), 36 selected parameters (AUROC=0.991, 0.884, and 0.839, respectively), and 20 selected parameters (AUROC=0.987, 0.877, and 0.817, respectively). In the validation cohort (n=37 202, HCC=2875), ridge regression had

TABLE 1. Parameters used in machine-learning models

Parameter	All 46 parameters	36 selected parameters	20 selected parameters
Male sex	✓	✓	✓
Age	✓	✓	✓
Platelet	✓	✓	✓
Albumin	✓	✓	✓
Total bilirubin	✓	✓	✓
Alanine aminotransferase	✓	✓	✓
Aspartate aminotransferase	✓	-	-
Alpha-fetoprotein	✓	-	-
International normalised ratio	✓	-	-
Creatinine	✓	-	-
Gamma glutamyl transferase	✓	-	-
Total cholesterol	✓	-	-
Glycated haemoglobin	✓	-	-
Fasting glucose	✓	-	-
Hepatitis B virus DNA	✓	-	-
Positive hepatitis B e-antigen	✓	-	-
Cirrhosis	✓	✓	✓
Cardiovascular disease	✓	✓	-
Colorectal cancer	✓	✓	-
Lung cancers	✓	✓	-
Urinary/renal malignancies	✓	✓	-
Cervical cancer	✓	✓	-
Breast cancer	✓	✓	-
Lymphoma	✓	✓	-
Chronic kidney disease	✓	✓	✓
Osteopenia	✓	✓	-
Osteoporosis	✓	✓	-
Diabetes mellitus	✓	✓	✓
Hypertension	✓	✓	✓
Anticoagulants	✓	✓	-
Angiotensin-converting-enzyme inhibitor / angiotensin receptor blocker	✓	✓	✓
Antiplatelet agents	✓	✓	✓
Beta blockers	✓	✓	✓
Histamine-2 receptor antagonist	✓	✓	-
Insulin	✓	✓	✓
Immunosuppressant	✓	✓	-
Loop diuretics	✓	✓	-
Metformin	✓	✓	✓
Nonsteroidal anti-inflammatory drug	✓	✓	-
Other lipid lowering agents	✓	✓	✓
Other oral hypoglycaemic agents	✓	✓	✓
Proton pump inhibitor	✓	✓	✓
Potassium sparing diuretics	✓	✓	-
Statins	✓	✓	✓
Sulphonylurea	✓	✓	✓
Thiazides	✓	✓	-

consistently higher accuracy with inclusion of all 46 parameters (AUROC=0.844), 36 selected parameters (AUROC=0.840), and 20 selected parameters (AUROC=0.821) [Table 2]. Sensitivity, specificity, and positive and negative predictive values of these five machine-learning models in training and validation cohorts are shown in Table 3. Dual cut-offs approach was applicable in >60% of patients in most models; the applicability was particularly high with random forest in the training cohort (96.6%) but not in the validation cohort (59.5%).

As the ridge regression model achieved consistently good performance in training and validation cohorts with all or selected parameters, the HCC ridge score was developed for comparison with other HCC risk scores. The low cut-off was set at <0.1 to achieve high sensitivity (≥90%) and between 0.1 and 0.2 to achieve high specificity (≥90%). The AUROC of the CU-HCC score, GAG-HCC score, REACH-B score, PAGE-B score, and REAL-B score was 0.672, 0.745, 0.671, 0.748, and 0.712, respectively (Table 4). Using dual cut-offs, the low cut-off of the REAL-B score (<4) had highest sensitivity (96.0%) but was applicable only to 17.6% of patients. The

TABLE 2. Area under the receiver operating characteristic curve (AUROC) of five machine-learning models in predicting hepatocellular carcinoma (HCC)

Machine-learning model	Training cohort (n=86 804, HCC=6821)			Validation cohort (n=37 202, HCC=2875)		
	20 selected parameters	36 selected parameters	All 46 parameters	20 selected parameters	36 selected parameters	All 46 parameters
	AUROC					
Logistic regression	0.814±0.006	0.829±0.006	0.825±0.006	0.818±0.009	0.832±0.009	0.829±0.009
Ridge regression	0.817±0.005	0.839±0.005	0.842±0.005	0.821±0.009	0.840±0.009	0.844±0.009
AdaBoost	0.822±0.006	0.828±0.006	0.828±0.006	0.824±0.009	0.833±0.009	0.832±0.009
Decision tree*	0.877±0.005	0.884±0.005	0.800±0.005	0.802±0.010	0.819±0.010	0.818±0.010
Random forest†	0.987±0.003	0.991±0.003	0.992±0.003	0.807±0.010	0.821±0.010	0.821±0.010

* AUROC higher than that of logistic regression and AdaBoost in both cohorts, P<0.05
† AUROC higher than that of decision tree in validation cohort, P<0.05

TABLE 3. Accuracy of five machine-learning models in predicting hepatocellular carcinoma

Machine-learning model	Dual Cut-offs	No. (%) of patients with <lower cut-off and ≥upper cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
			% (95% confidence interval)			
Training cohort (n=86 804)*						
Logistic regression	0.18	43 951 (50.6)	0.90 (0.89-0.91)	0.54 (0.542-0.545)	0.143 (0.141-0.146)	0.985 (0.983-0.985)
	0.29	11 527 (13.3)	0.52 (0.51-0.53)	0.90 (0.898-0.902)	0.307 (0.300-0.315)	0.956 (0.955-0.958)
Ridge regression	0.07	48 341 (55.7)	0.90 (0.89-0.91)	0.596 (0.593-0.599)	0.160 (0.156-0.164)	0.986 (0.985-0.987)
	0.15	11 506 (13.3)	0.52(0.51-0.53)	0.900 (0.898-0.902)	0.307 (0.300-0.315)	0.956 (0.955-0.958)
AdaBoost	0.42	43 298 (49.9)	0.91 (0.90-0.92)	0.533 (0.529-0.536)	0.142 (0.140-0.145)	0.985 (0.984-0.986)
	0.45	10 363 (11.9)	0.48 (0.46-0.49)	0.911 (0.909-0.913)	0.313 (0.308-0.320)	0.953 (0.952-0.954)
Decision tree	0.04	48 765 (56.2)	0.92 (0.92-0.93)	0.603 (0.599-0.606)	0.166 (0.163-0.170)	0.990 (0.989-0.991)
	0.17	12 029 (13.9)	0.63 (0.62-0.64)	0.903 (0.902-0.905)	0.356 (0.349-0.363)	0.966 (0.965-0.967)
Random forest	0.45	71 804 (82.7)	0.90 (0.90-0.91)	0.998 (0.997-0.998)	0.976 (0.973-0.979)	0.992 (0.991-0.992)
	0.10	12 074 (13.9)	0.97 (0.96-0.97)	0.932 (0.930-0.933)	0.547 (0.539-0.557)	0.997 (0.997-0.998)
Validation cohort (n=37 202)						
Logistic regression	0.18	19 448 (52.3)	0.90 (0.89-0.91)	0.568 (0.553-0.565)	0.146 (0.142-0.151)	0.985 (0.984-0.987)
	0.29	4930 (13.3)	0.52 (0.50-0.54)	0.900 (0.896-0.902)	0.304 (0.293-0.317)	0.957 (0.955-0.959)
Ridge regression	0.07	20 816 (56.0)	0.90 (0.89-0.91)	0.598 (0.593-0.603)	0.158 (0.152-0.164)	0.986 (0.985-0.988)
	0.15	4932 (13.3)	0.52 (0.50-0.54)	0.900 (0.897-0.903)	0.304 (0.291-0.317)	0.957 (0.955-0.960)
AdaBoost	0.42	18 725 (50.3)	0.91 (0.90-0.92)	0.538 (0.532-0.543)	0.142 (0.137-0.146)	0.987 (0.985-0.988)
	0.45	4377 (11.8)	0.47 (0.45-0.49)	0.912 (0.909-0.914)	0.310 (0.297-0.323)	0.954 (0.952-0.956)
Decision tree	0.02	17 689 (47.6)	0.90 (0.89-0.91)	0.507 (0.501-0.511)	0.133 (0.129-0.137)	0.983 (0.982-0.985)
	0.17	4987 (13.4)	0.54 (0.52-0.56)	0.900 (0.897-0.904)	0.312 (0.302-0.330)	0.959 (0.957-0.961)
Random forest	0.01	17 561 (47.2)	0.90 (0.89-0.91)	0.503 (0.496-0.508)	0.132 (0.127-0.137)	0.984 (0.982-0.986)
	0.20	4561 (12.3)	0.52 (0.50-0.53)	0.910 (0.907-0.913)	0.326 (0.312-0.341)	0.957 (0.955-0.959)

* Dual cut-offs are selected to achieve >90% sensitivity and specificity

TABLE 4. Comparison of the hepatocellular carcinoma (HCC) ridge score and other HCC risk scores in predicting HCC in the validation cohort (n=37 202)

Risk score	Area under the receiver operating characteristic curve	Dual Cut-offs	No. (%) of patients with <lower cut-off and ≥upper cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value
				% (95% confidence interval)			
HCC ridge score	0.840	0.07	20 816 (56.0)	90.0 (89.0-0.91)	59.8 (59.3-60.3)	15.8 (15.2-16.4)	98.6 (98.5-98.8)
		0.15	4932 (13.3)	52.2 (50.3-54.0)	90.0 (89.7-90.3)	30.4 (29.1-31.7)	95.7 (95.5-96.0)
CU-HCC score	0.672	<5	27 083 (72.8)	46.4 (28.6-64.3)	74.0 (69.9-78.4)	10.3 (6.4-14.3)	95.6 (94.2-97.1)
		≥20	7812 (21.0)	32.1 (14.3-50.0)	79.7 (75.9-83.6)	9.1 (4.5-14.0)	94.8 (93.6- 96.2)
GAG-HCC score	0.745	<80	25 781 (69.3)	64.3 (46.4-82.1)	71.5 (67.2-75.6)	12.3 (8.8-15.9)	97.0 (95.5-98.4)
		≥101	2939 (7.9)	28.6 (14.3-46.4)	93.4 (91.1-95.6)	21.1 (10.5-33.3)	95.5 (94.5-96.6)
REACH-B score	0.671	<8	18 601 (50.0)	72.7 (54.6-90.9)	52.8 (45.4-59.7)	16.2 (12.1-20.0)	94.1 (89.8-97.9)
		≥14	558 (1.5)	4.5 (0-13.5)	98.9 (97.4-100)	33.3 (0-100)	89.2 (88.7-90.2)
PAGE-B score	0.748	<10	10 193 (27.4)	95.7 (94.9-96.5)	29.4 (28.9-30.0)	10.7 (10.6-10.9)	98.7 (98.5-99.0)
		≥13	17 969 (48.3)	81.1 (79.4-82.7)	54.6 (54.0-55.3)	13.7 (13.4-14.0)	97.0 (96.8-97.3)
REAL-B score	0.712	<4	6548 (17.6)	96.0 (95.2-96.9)	19.2 (18.5-19.8)	12.0 (11.9-12.2)	97.7 (97.2-98.2)

Abbreviations: CU-HCC = Chinese University-HCC; GAG-HCC = guide with age, gender, hepatitis B virus DNA, central promoter mutations and cirrhosis-HCC; PAGE-B = platelets, age, gender, and hepatitis B virus; REACH-B = risk estimate for hepatocellular carcinoma in chronic hepatitis B; REAL-B = real-world effectiveness from the Asia Pacific rim liver consortium for hepatitis B virus

high cut-off of the REACH-B score (≥14) had highest specificity (98.9%) but was applicable only to 1.5% of patients. The HCC ridge score achieved larger AUROC (0.840) and higher applicability, with 30.7% of patients falling into the grey zone.

Discussion

Machine-learning models of ridge regression and random forest are accurate to predict HCC in patients with CVH. These models may be used as built-in functional keys or calculators in electronic health systems to facilitate hepatitis elimination. Electronic health records provide robust and comprehensive demographic and laboratory data of patients. Nonetheless, clinical observations and anthropometric measurements may be missing, especially in regions where manual data entry is not available.

Machine-learning models can be applied in managing patients with CVH, which affects >300 million people worldwide. Ridge regression is a technique for analysing multiple regression data that have multicollinearity problems. When multicollinearity occurs, least squares estimates are unbiased, but their variances are large and may deviate far from the true value. Hence, ridge regression is particularly suitable for machine-learning models in clinical medicine, as many parameters included in the models are closely related and with multicollinearity.

Conclusion

The HCC ridge score accurately predicts HCC in CVH patients. Machine-learning models may be developed as built-in functional keys or calculators in electronic health systems to reduce cancer mortality. Studies comparing machine-learning-model-guided HCC surveillance with routine clinical practice for early diagnosis of HCC in CVH patients are warranted.

Funding

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Disclosure

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Diagnostic accuracy of tele-ophthalmology versus face-to-face consultation: abridged secondary publication

KC Shih *, JKW Wong, JX Lian, CLK Lam, JSM Lai

KEY MESSAGES

1. Tele-ophthalmology highly agrees with face-to-face consultation in the diagnosis and grading of cataracts, glaucoma, and age-related macular degeneration (AMD).
2. Tele-ophthalmology is highly sensitive and specific for AMD, highly specific but less sensitive for cataracts, and highly sensitive but less specific for glaucoma.
3. Tele-ophthalmology results in higher downstream costs than face-to-face consultation, because tele-ophthalmology over-diagnoses cataracts and its severity.

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Introduction

Telemedicine is a viable care model during the COVID-19 pandemic. Tele-ophthalmology has benefits in healthcare beyond the pandemic.[1] Timely diagnosis and treatment of ocular diseases may prevent blindness. Tele-ophthalmology enables access to specialist health care services by underprivileged and disabled patients in areas with limited expertise. Nonetheless, tele-ophthalmology has been mostly used for screening a single disease such as diabetic retinopathy.[2] The accuracy of tele-ophthalmology for various diseases has not been established, although tele-ophthalmology and face-to-face consultation are comparable in terms of diagnostic outcomes.[3,4] Previous studies of tele-ophthalmology are limited by the lack of robust clinical trials, small sample sizes, and absence of quality data, making assessment of economical and clinical benefits difficult.

This study aims to determine the diagnostic accuracy of tele-ophthalmology for cataracts, glaucoma, and age-related macular degeneration (AMD), with face-to-face consultation as the gold standard, and to compare tele-ophthalmology with face-to-face consultation in terms of diagnosis, severity, and downstream costs.

Methods

This prospective comparative study was conducted between 1 August 2019 and 31 July 2021. Consecutive patients aged ≥40 years who were referred to the specialist ophthalmology clinic of Grantham Hospital, Hong Kong for blurred vision of ≥3 months were recruited. Those with a history of diabetes, inability to communicate verbally, or acute eye symptoms or ocular trauma requiring immediate ophthalmic care were excluded, as were those with un-readable slit lamp or retina images.

Participants underwent face-to-face consultation by an ophthalmologist for medical history taking, slit-lamp biomicroscopy, intraocular pressure measurement via applanation tonometry, mydriatic retinal examination with an indirect ophthalmoscope, and completion of the assessment form A. An optometrist performed a Snellen Chart distant visual acuity test with pinhole. Cataract was defined as cloudiness and/or yellow discoloration of the crystalline lens. Glaucoma was defined as pathological cupping of the optic disc. AMD was defined as the presence of drusen, geographical atrophy (dry AMD), and/or choroidal neovascularisation in the macular area (wet AMD).

For the tele-ophthalmology arm, a store-and-forward consultation model was used. The ophthalmologist completed the assessment form B after assessing the clinical data and ocular images that were collected by others. The optometrist captured colour photos of the anterior segment of the eye through a digital compact camera attached to a slit lamp biomicroscope. Anterior segment photographs were captured under low magnification (7.5x), with diffuse illumination of the cornea and the bulbar conjunctiva and parallelepiped section of the corneal stroma and central anterior chamber. Digital photographs of the retina that covered two standard fields and focused on the optic disc and macula were taken with a mydriatic fundus camera.

The pinhole visual acuity (VA), intraocular pressure (IOP), and referral letter were transmitted to the ophthalmologist.

Statistical analysis was performed using SPSS (Windows version 27.0; IBM Corp, Armonk [NY], US). The prevalences of cataract, glaucoma, and AMD, and their severity based on face-to-face consultation and tele-ophthalmology were compared using the Chi-squared test or post hoc test. The agreements between face-to-face consultation and tele-ophthalmology in terms of diagnosis and severity of cataracts, glaucoma, and AMD were assessed using the Cohen's Kappa statistic. Diagnostic accuracy (sensitivity, specificity, and positive and negative predictive values) of tele-ophthalmology was calculated, with face-to-face consultation as the gold standard. Improvement in agreement and diagnostic accuracy by adding VA or IOP data was determined. A two-tailed P value of <0.05 was considered statistically significant.

Results

A total of 860 eyes from 248 women and 182 men were assessed. The mean age of participants was 67±11 years. The two ophthalmologists took turns for face-to-face consultation and tele-ophthalmology for 44.9% and 55.1% of the time, respectively.

Using face-to-face consultation as the gold standard for diagnosis, 75.3% of eyes had cataracts, 31.6% of eyes had possible glaucoma, and 12.4% of eyes had AMD (Table 1). Agreement between face-to-face consultation and tele-ophthalmology was high across all three ocular diseases (Table 2). Additional VA data for cataract significantly improved the agreement from 79% to 89% in cataract severity, but additional VA and IOP data did not improve agreement in other diseases.

Diagnostic accuracy of tele-ophthalmology was highest for AMD, with >99% sensitivity and specificity. For cataract, the specificity was >99% but the sensitivity was 87.3%, which improved to 87.8% after adding VA data. For glaucoma, the sensitivity was >98% but the specificity was 75.7%, which improved to 76.5% after adding IOP data (Table 3).

The estimated cost per patient per 6 months was higher for tele-ophthalmology than for face-to-face consultation, with a difference of HK$547.16 (US$70.24) when VA and IOP data were not added. The difference was HK$99.86 (US$12.82) when VA and IOP data were added.

Discussion

The agreement was high between face-to-face consultation and tele-ophthalmology in terms of diagnosis and severity of cataracts, glaucoma, and AMD. In experienced ophthalmologists, diagnosis and severity can be accurately determined through slit lamp and fundus images alone and can be further improved by adding VA and IOP data. The lower agreement levels for glaucoma and cataracts were likely due to the inability of the current imaging techniques to differentiate subtle differences in disease stages and to identify early disease forms.

Tele-ophthalmology was highly sensitive and specific for AMD (both >99%). In diagnosing cataracts, the sensitivity was 87.3%, which was likely due to the relatively inconspicuous appearance of early cataracts, in that the 'yellowing' of the lens can

TABLE 1. Prevalence of cataract, glaucoma, and age-related macular degeneration (AMD) based on face-to-face consultation or tele-ophthalmology

Ocular disease	Prevalence, %			χ^2 statistic	P value
	Face-to-face consultation	Tele-ophthalmology (without visual acuity and intraocular pressure data)	Tele-ophthalmology (with visual acuity and intraocular pressure data)		
Cataracts	75.3 (671/860)	80.4 (691/860)	80.2 (690/860)	1.8	0.400
Early	64.4 (432/671)	60.6 (419/691)	64.4 (444/690)		
Moderate	31.7 (213/671)	36.0 (249/691)	32.5 (224/690)		
Severe	3.6 (24/671)	3.33 (23/691)	3.19 (22/690)		
Possible glaucoma	31.6 (272/860)	24.9 (214/860)	25.12 (216/860)	12.6	0.002
Glaucoma suspect	84.6 (230/272)	91.1 (195/214)	90.2 (193/216)		
Definite glaucoma	17.6 (48/272)	8.88 (19/214)	10.7 (23/216)		
AMD	12.4 (107/860)	12.3 (106/860)	12.3 (106/860)	0.1	1.000
Drusen only	53.3 (57/107)	58.5 (62/106)	58.5 (62/106)		
Dry AMD	22.4 (24/107)	14.2 (15/106)	14.2 (15/106)		
Dry AMD with geographical atrophy	21.5 (23/107)	23.6 (25/106)	23.6 (25/106)		
Wet AMD	2.80 (3/107)	3.70 (4/106)	3.70 (4/106)		

TABLE 2. Agreement between tele-ophthalmology and face-to-face consultation in terms of diagnosis and severity of cataract, glaucoma, and age-related macular degeneration (AMD)

Diagnosis and severity	Agreement, %	Kappa value (95% confidence interval)	P value
Cataract			
Diagnosis			
Without visual acuity data	96.7 (832/860)	0.90 (0.86-0.93)	<0.001
With visual acuity data	96.9 (833/860)	0.91 (0.87-0.94)	<0.001
Severity			
Without visual acuity data	86.5 (744/860)	0.79 (0.75-0.82)	<0.001
With visual acuity data	93.2 (800/860)	0.89 (0.86-0.92)	<0.001
Glaucoma			
Diagnosis			
Without intraocular pressure data	91.7 (789/860)	0.79 (0.74-0.84)	<0.001
With intraocular pressure data	91.9 (790/860)	0.80 (0.75-0.84)	<0.001
Severity			
Without intraocular pressure data	88.1 (758/860)	0.72 (0.66-0.77)	<0.001
With intraocular pressure data	88.9 (765/860)	0.74 (0.69-0.78)	<0.001
AMD			
Diagnosis			
Without visual acuity data	99.2 (853/860)	0.96 (0.93-0.99)	<0.001
With visual acuity data	99.2 (853/860)	0.96 (0.93-0.99)	<0.001
Severity			
Without visual acuity data	97.3 (837/860)	0.88 (0.84-0.93)	<0.001
With visual acuity data	97.3 (837/860)	0.88 (0.84-0.93)	<0.001

TABLE 3. Diagnostic accuracy of tele-ophthalmology for cataract, glaucoma, and age-related macular degeneration (AMD)

Ocular disease	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Cataract (without visual acuity data)	87.3	99.4	97.6	96.5
Cataract (with visual acuity data)	87.8	99.4	97.6	96.7
Glaucoma (without intraocular pressure data)	98.7	75.7	90.2	96.3
Glaucoma (with intraocular pressure data)	98.7	76.5	90.5	96.3
AMD (without visual acuity data)	99.7	99.5	99.3	98.1
AMD (with visual acuity data)	99.7	99.5	99.3	98.1

be very subtle and may not be adequately captured on slit lamp photographs. In diagnosing glaucoma, the specificity was 75.7%, which was likely due to the use of two-dimensional retinal photographs for assessment of optic disc cupping. Without stereopsis, the cupping is less adequately evaluated. A study that used stereoscopic images of the optic nerve head reported accurate remote diagnosis and monitoring of glaucoma.[5] However, this type of fundus camera is not yet commercially viable for primary care settings in Hong Kong.

Tele-ophthalmology was more costly per patient per 6 months than face-to-face consultation, with a difference of US$12.82, because tele-ophthalmology over-diagnosed cataracts and its severity. Diagnostic accuracy is the most important determinant on the cost-effectiveness of tele-ophthalmology in the long run. In addition, the potential medicolegal costs and loss of quality of life that unnecessary cataract surgeries and missed glaucoma secondary to tele-ophthalmology should be considered.

Conclusions

Tele-ophthalmology is accurate and viable alternative for face-to-face consultation, but it still has diagnostic

and grading limitations, particularly for cataracts and glaucoma. The accuracy of tele-ophthalmology can be improved by using high-resolution cameras in primary care and using machine learning to aid diagnosis and management.

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Disclosure

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1. Wong JK, Zhu MM, Lam JC, et al. Prospective comparative study investigating agreement between tele-ophthalmology and face-to-face consultations in patients presenting with chronic visual loss. Ophthalmol Ther 2022;11:1199-213.

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Foreign language training via mobile application to improve cognitive functions in patients with mild cognitive impairment: abridged secondary publication

PCM Wong *, SYC Tsang, Z Deng, M Antoniou

KEY MESSAGES

1. Foreign language training in community centres has been reported to improve cognitive functions of older adults with mild cognitive impairment.
2. There is evidence of an overall effectiveness of foreign language training on the Alzheimer's Disease Assessment Scale–cognitive subscale score with a medium effect size.
3. Foreign language training may boost cognitive functions in older adults with below-average cognitive abilities; whether long-term or short-term training is more beneficial requires further studies.

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Introduction

Computer-based foreign language (FL) training in a community centre has been reported to promote cognitive health in older adults.[1] The current study aims to compare the effect of FL training on promotion of cognitive functions. We hypothesise that FL training via a mobile application may engage the whole episodic memory brain network and promote positive neurophysiological changes potentially via neuronal modification and repair processes.[2,3] In addition, we hypothesise that cognitive improvement is greater after long-term training than short-term training even if the overall training duration is identical.

Methods

Native Cantonese speakers with no functional knowledge of English aged 60 to 80 years with mild cognitive impairment who had (1) basic literacy skills and completed at least 6 years of primary school education, (2) no significant psychiatric or neurological deficits or hearing difficulties, and (3) no experience with the Rosetta Stone language learning software were included. Mild cognitive impairment was defined as (1) a score of 0.5 or 1 on the Clinical Dementia Rating scale[4] or (2) a score of 0 on the Clinical Dementia Rating scale and 25% standard deviation below the age-typical mean on the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) or the Category Verbal Fluency Test.

Of 258 persons screened, 158 fulfilled the inclusion criteria. Of them, 15 decided not to enrol and the remaining 143 were randomly assigned to four groups: centre FL, long-term mobile FL, short-term mobile FL, or music listening (control).

The three FL groups learned English using the Rosetta Stone language learning software. The centre FL and long-term mobile FL groups spent 1 hour per day, 5 days per week for 6 months. The short-term mobile FL group spent 2 hours per day, 5 days per week for 3 months. The centre FL group went to elderly centres for training, whereas the mobile FL groups installed a mobile application and were taught to use it by a research assistant. The music listening group spent 2 hours per day, 5 days per week for 3 months for music listening using a mobile phone.

The primary outcome measure was the ADAS-Cog. Secondary outcome measures included the Auditory Reading Span, the Boston Naming Test, the Wechsler Digit Span task (forward and backward), the Attention Network Test, and the Short-Form 12-item Health Survey. An intent-to-treat approach was used for statistical analysis. For each of the outcome measures, a 2 (group) × 2 (time) analysis of variance was conducted.

Results

Of 143 participants enrolled, 80 completed the study and were assessed at the endpoint. The dropout rate was 44.06%, because community centres were closed

at different times during the COVID-19 pandemic.

There was no significant difference in baseline variables between the centre FL and the long-term mobile FL groups. Main effects of time were found on Auditory Reading Span, Clinical Dementia Rating scale, and Category Verbal Fluency Test. No one type of FL training was more effective than the others.

There was no significant difference in baseline variables between the long-term and short-term mobile FL groups. Significant interactions were found on the Boston Naming Test and Attention Network Test reaction time (neutral). From baseline to endpoint, performance in the Boston Naming Test deteriorated in the long-term mobile FL group and improved in the short-term mobile FL group, whereas reaction time in the Attention Network Test deteriorated in the long-term mobile FL group and improved in the short-term mobile FL group. Main effects of time were found on ADAS-Cog, Auditory Reading Span, Clinical Dementia Rating scale, and Category Verbal Fluency Test.

There was a significant difference in baseline ADAS-Cog score between the short-term mobile FL group and the music listening group. A significant interaction was found on the Attention Network Test. From baseline to endpoint, reaction time of Attention Network Test improved in the short-term mobile FL group and deteriorated in the music listening group. Main effects of time were found on ADAS-Cog, Boston Naming Test, Clinical Dementia Rating scale, Wechsler Digit Span, and Attention Network Test. FL improved cognitive performance more than music listening did but only in Attention Network Test.

To assess simple effects (as opposed to comparative training effects) of FL training, we conducted t-tests on ADAS-Cog of each group. FL training had a significant effect with a medium effect size (Cohen's d=0.422). In contrast, music listening did not result in a significant effect with a small effect size (Cohen's d=0.229) [Fig].

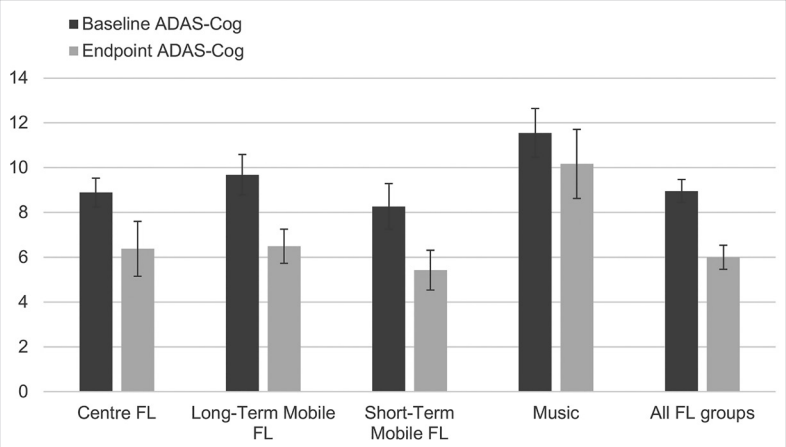

FIG. Baseline and endpoint scores of the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) in foreign language (FL) training groups and music listening (control) group

Discussion

Because of a large dropout rate, it was not possible to determine whether FL training via mobile application results in cognitive benefits and whether long-term and short-term FL training results in different cognitive benefits. Nevertheless, we found evidence of an overall effectiveness of FL training on ADAS-Cog with a medium effect size. Long-term FL training yielded a larger effect size (Cohen's d=0.599) than short-term FL training (Cohen's d=0.497), but this difference did not reach statistical significance. Music listening did not improve cognitive abilities.

FL training may be a cognitively stimulating activity that boosts cognitive functions in older adults with below-average cognitive abilities, evidenced by simple training effects (relative to baseline) with a medium effect size. However, whether long-term FL training would produce a larger effect than short-term FL training requires further investigation.

Funding

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High-dimensional machine learning to predict hospital readmission among older people with chronic kidney disease: abridged secondary publication

Q Zhang *, E Leung, JTF Lau, KKF Tsoi, HY So, WWS Ho, SCY Cheung

KEY MESSAGES

1. A novel factorisation-based machine-learning model, which is Hong Kong–weighted with fuzzy partition, is proposed to predict the risk of hospital readmission among patients with chronic kidney disease.
2. This is one of the first machine-learning models for readmission prediction based on territory-wide data in Hong Kong.
3. Application of this model may help reduce the cost of hospital management and improve the quality of life among patients with chronic kidney disease.

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Introduction

Over 20% of older people experience unexpected readmission to accident and emergency department within 1 month of discharge. Identifying at-risk patients is important in geriatric medical care planning. However, in older people with multiple chronic diseases, traditional screening methods or basic machine-learning algorithms are difficult to identify disease risk patterns. We developed a Hong Kong–weighted factorisation machine with fuzzy partition (wFMFP) to predict the risk of readmission among patients with chronic kidney disease (Fig 1).

Methods

A total of 418 305 admission records of 19 457 older patients aged ≥65 years with chronic kidney disease as the primary diagnosis between 2008 and 2017 in Hong Kong public hospitals were retrieved. Of the 418 305 admission records, 392 863 (12 046 patients) were within 30 days of previous discharge to home. Of the 12 046 patients, 4523 (37.55%) had a single readmission and 7523 (62.45%) had multiple readmissions. Data collected included age, district of residence, admission specialty (medicine or clinical oncology), length of stay (LOS), source of admission (emergency department, other hospital, or others), triage category at the emergency department (critical, emergency, urgent, semi-urgent, non-urgent), subacute care (yes or no), LOS of the subacute care, total quantity of drug dispensed, and total prescribed dispensing duration (days).

Among 12 046 patients readmitted within 30 days, the mean patient age was 72.35 years; the mean LOS was 1.4360 days; the mean total quantity of drug dispensed was 14.4189 doses; and the mean total prescribed dispensing duration was 8.7560 days. There were 386 362 admissions to medicine specialties and 51 admissions to oncology specialties. The most common triage category at emergency departments was urgent (42.05%), followed by semi-urgent (26.07%), emergency (17.78%), non-urgent (13.48%), and critical (0.62%). The mean LOS of subacute care was 17.5550 days. The mean haemoglobin A1c was 52.5285 mmol/mol.

Factorisation machines provide a general predictor that can efficiently model high-order interactions among explanatory features in linear time complexity.[1] Matrix factorisation decomposes a matrix into matrices. Tensor factorisation is the high-order extension of matrix factorisation; it enables modelling of heterogeneous and multidimensional data.[2] Matrix and tensor factorisations can extract the latent components to enhance data-mining tasks. In this project, CANDECOMP/PARAFAC factorisation was used for prediction. The admission count was used to construct tensors in the proposed models, and non-negative tensor factorisation methods using generalised Kullback-Leibler divergence and multiplicative update rules were followed.[2,3]

Traditional regression methods usually add clinical attributes as independent variables, ignoring the high-dimensional interrelations and high-order interactions between clinical attributes and diseases. Tensor factorisation provides a powerful framework

to model such multi-aspect data by explicitly exploiting the high-dimensional structure to identify latent clusters of data.[2,3] In this project, we used tensor factorisation to evaluate the risks of all chronic diseases. For each patient, tensor factorisation produced a ranked list of chronic diseases according to predicted risk scores. Risk scores for different diseases in such a rank were used as predictors in a traditional machine-learning model to predict the risk of readmission within a certain period (30 days, 90 days, 1 year).

In the wFMFP model, step 1 is to initialise the number of clusters (equal to the number of sub-wFM models) and the overlap parameter η for training data segmentation. Step 2 is to use fuzzy c-means to obtain membership μis, cluster centres β_s in (1), and the spread width δ_s^q in (2). Step 3 is to repeat step 2 when the stop criterion is not satisfied; otherwise, continue to step 4. Step 4 is to obtain training subsets Ds in (3) according to the generated centres and the spread width through fuzzy c-means. Step 5 is to construct sub-wFM prediction models. Step 6 is to generate the overall prediction output of wFMFP by using (4) with fuzzy weighting mechanism in (5).

$$\mu_{is} = \frac{\left(1/\|\vec{x}_i - \vec{\beta}_s\|^2\right)^{1/(z-1)}}{\sum_{s=1}^{S}\left(1/\|\vec{x}_i - \vec{\beta}_s\|^2\right)^{1/(z-1)}}, \quad \vec{\beta}_s = \frac{\sum_{i=1}^{N}\mu_{is}^z \vec{x}_i}{\sum_{i=1}^{N}\mu_{is}^z}. \tag{1}$$

$$\delta_s^q = \sqrt{\frac{\sum_{i=1}^{N}\mu_{is}^z \|x_i^q - x_s^q\|^2}{\sum_{i=1}^{N}\mu_{is}^z}}, \; q = 1, 2, \cdots, Q \text{ and } s = 1, \cdots, S. \tag{2}$$

$$\mathcal{D}_s = \{X_s, Y_s\} = \{(\vec{x}_i, y_i) | \beta_s^q - \eta\delta_s^q \le x_i^q \le \beta_s^q + \eta\delta_s^q\}, \; s = 1, \cdots, S \tag{3}$$

$$\hat{y}(\vec{x}_i) = \frac{\sum_{s=1}^{S}\omega_s(\vec{x}_i)\cdot wFM_s(\vec{x}_i)}{\sum_{s=1}^{S}\omega_s(\vec{x}_i)}, \; i = 1, 2, \cdots, N. \tag{4}$$

$$\omega_s^q(x_i^q) = \max\left(\min\left(\frac{x_i^q(\beta_s^q - \eta\delta_s^q)}{\beta_s^q - (\beta_s^q - \eta\delta_s^q)}, \frac{(\beta_s^q + \eta\delta_s^q) - x_i^q}{(\beta_s^q + \eta\delta_s^q) - \beta_s^q}\right), 0\right)$$

$$i = 1, 2, \cdots, N, q = 1, 2, \cdots, Q, s = 1, 2, \cdots, S \tag{5}$$

Performance of wFMFP and other models (factorisation machine with fuzzy partition, factorisation machine, polynomial kernel-based support vector machine, sigmoid kernel-based support vector machine, radial basis function kernel-based support vector machine, and multilayer perceptron) was evaluated by coefficient of determination (R^2), mean squared error, mean absolute error, mean absolute percentage error, and median absolute percentage error. Higher R^2 and lower mean squared error, mean absolute error, mean absolute percentage error, and median absolute percentage error indicate better performance of prediction.

Results

Correlation analysis between readmission variables is shown in Fig 2. wFPFM outperformed other models in predicting readmission risk when the number of training subsets was >5 (Table).

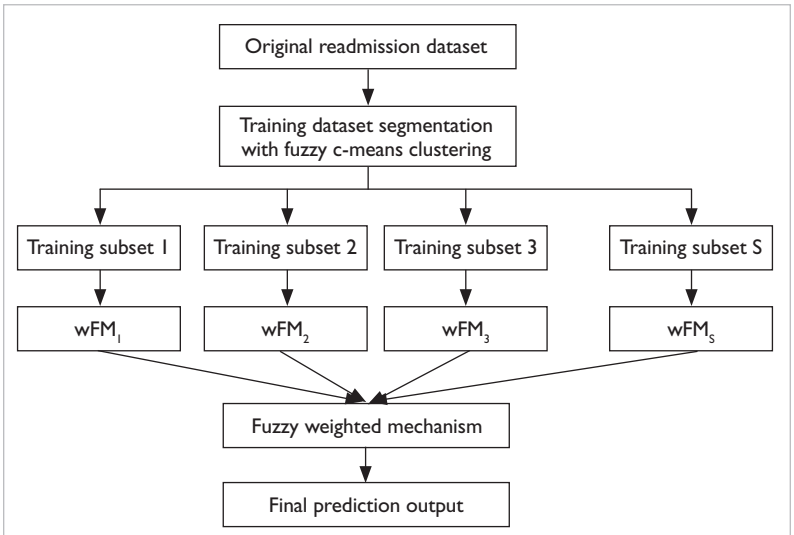

FIG 1. The architecture of weighted factorisation machine (wFM) with fuzzy partition

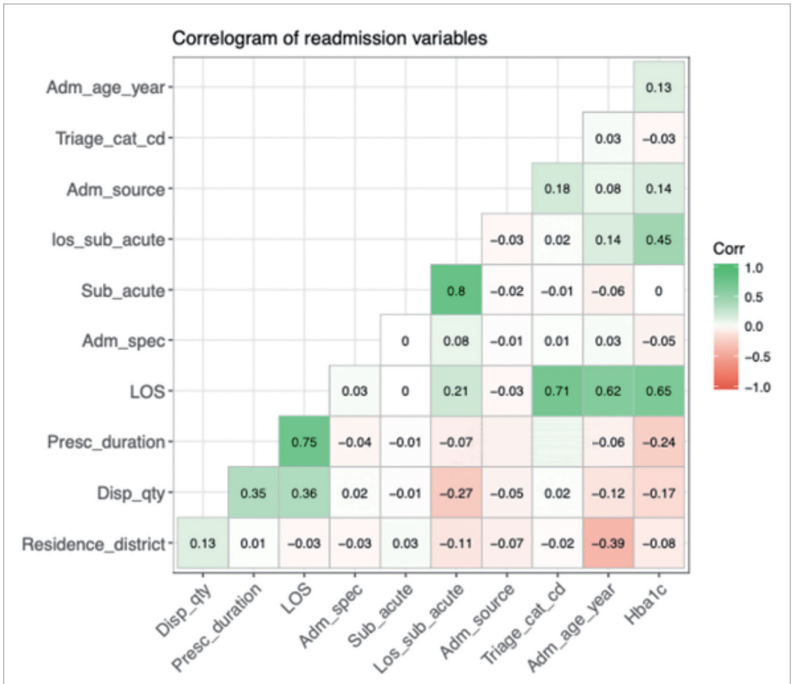

FIG 2. Correlation analysis between readmission variables

Discussion

The wFMFP can deal with the boundary effects and data sparsity issue. In the present study, the wFMFP was superior to other models in predicting readmission risk of patients with chronic kidney disease. The wFMFP can be used as an integral component of the decision support system to better characterise, forecast, and provide preventive

TABLE. Performance of weighted factorisation machine with fuzzy partition (wFMFP) and other machine-learning models in predicting the risk of hospital readmission among patients with chronic kidney disease

Model	R^2	Mean squared error	Mean absolute error	Mean absolute percentage error	Median absolute percentage error
wFMFP					
3 wFMs	0.8267	0.2764	0.2692	0.2458	2521
4 wFMs	0.8518	0.2256	0.2263	0.2390	0.2338
5 wFMs	**0.8865**	**0.2181**	0.2411	0.2311	**0.2130**
6 wFMs	0.8762	0.2512	**0.2142**	**0.2265**	0.2286
7 wFMs	0.8336	0.2292	0.2295	0.2389	0.2421
8 wFMs	0.8349	0.2277	0.2221	0.2459	0.2333
9 wFMs	0.8101	0.2305	0.2322	0.2474	0.2605
10 wFMs	0.7758	0.2471	0.2302	0.2528	0.2747
Factorisation machine with fuzzy partition					
3 FMs	0.7947	0.2633	0.2593	0.2836	0.2994
4 FMs	0.8019	0.2773	0.2667	0.2787	0.2856
5 FMs	0.8249	0.2628	0.2584	0.2924	0.3172
6 FMs	0.8383	0.2649	0.2854	0.2833	0.3174
7 FMs	0.8052	0.2734	0.2621	0.2881	0.3130
8 FMs	0.8495	0.2624	0.2973	0.2856	0.3127
9 FMs	0.7942	0.2735	0.3133	0.3000	0.3245
10 FMs	0.7538	0.2863	0.2973	0.3158	0.3182
Weighted factorisation machine	0.8318	0.2368	0.2656	0.2916	0.3276
Factorisation machine	0.7966	0.2490	0.2931	0.2984	0.3105
Polynomial kernel-based support vector machine	0.7718	0.2948	0.3172	0.2934	0.3123
Sigmoid Kernel-based support vector machine	0.7348	0.2817	0.3291	0.2942	0.3027
Radial basis function kernel-based support vector machine	0.7943	0.2771	0.3012	0.2987	0.3120
Multilayer perceptron	0.7943	0.2771	0.3012	0.2987	0.3220

guideline for readmission risk management. The wFMFP can be used for assessment of discharge and readmission risk. Outcomes from wFMFP can provide a prediction of the explicit risk factors of each patient, which helps decide the disease management strategy such as discharge or intensive medical care for a certain disease. Implementation of predictive readmission analytics provides hospitals an easy-to-use readmission management tool for healthcare cost reduction, efficiency improvement, and lowering LOS deviation. For patients, the model can assist in the domestic care and provide guidance in lifestyle. For example, patients with high risk of readmission because of diabetes should pay attention to daily glucose control. In addition, the wFMFP can be extensively used in various prediction and classification tasks in other domains (transportation, finance).

We plan to examine the prediction performance differences of wFMFP with different weighted strategies, especially when we assign weights through clustering algorithms. We also plan to conduct comparative analysis of the performance of wFMFP under different loss functions. We also plan to investigate solutions to improve the performance of wFMFP in parallel computing settings to practical use once the real-time model training is needed.

Funding

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Disclosure

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1. Zhou J, Li X, Wang X, Chai Y, Zhang Q. Locally weighted factorization machine with fuzzy partition for elderly readmission prediction. Knowl Based Syst 2022;242:108326.

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Cost-effectiveness of screening and management strategies for chlamydia control in Hong Kong: abridged secondary publication

WCW Wong *, C Wong, J Ong, C Fairley, J Hocking

KEY MESSAGES

1. *Chlamydia trachomatis* is the most common bacterial sexually transmitted infection worldwide. Untreated infections can lead to onward transmission and serious complications.
2. Cost and staff attitude are the most important factors for patients to test and treat chlamydia, respectively.
3. Targeted testing with strengthened contact tracing is the most cost-effective way to reduce the prevalence of chlamydia in the general population.
4. Upskilling primary care to identify at-risk individuals may improve efficiency and cost-effectiveness of any future chlamydia testing programmes in Hong Kong.

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Introduction

Chlamydia trachomatis is the most common bacterial sexually transmitted infection (STI) worldwide. Untreated infections can lead to onward transmission and serious complications to women, pregnant women, newborn, and men. Its prevalences in sexually active young women and men (aged 18 to 26 years) and middle-aged women (aged 40 to 49 years) in Hong Kong are comparable to those in the west.[1] The effectiveness of population and opportunistic screening programmes in reducing the burden of chlamydia is mixed. Recent focus has shifted from universal screening to a more targeted approach of strengthening patient testing and linkage-to-care.[2]

Discrete choice experiment quantitatively captures consumer preferences and can be used to predict the uptake of various detection and management programmes. Mathematical modelling can evaluate the efficacy and cost-effectiveness of health interventions. Recent advancements on modelling chlamydia control strategies enable evaluation of hypothetical strategies without actual implications on resources and manpower. This study aims to quantify the preferences of sexually active people in Hong Kong for the uptake of chlamydia testing services and management (if diagnosed), and to evaluate the cost-effectiveness of various chlamydia control strategies.

Methods

Individuals living in Hong Kong aged >18 years who reported having vaginal/anal sex in the past 12 months were invited to participate in the survey. Members of an online panel whose profile matched the sample frame were invited to participate through email. Participants were asked about their preferences for chlamydia testing and management services. Their sociodemographic characteristics, sexual behaviours, testing history for chlamydia, and attitudes towards contact tracing were collected. Preference data were analysed using random parameters logit models. Interactions for attribute levels with significant coefficients and standard deviations were presented, and the probabilities of people choosing not to opt out under various scenarios were estimated. The impact of altering attributes from the status quo was examined.

A model that could represent dynamics of highly connected individuals, contain flexible options for treatment-seeking, and include variable delays and options for partner notification was developed to examine the cost-effectiveness of chlamydia control strategies. The baseline scenario was derived from local chlamydia statistics. Population of interest were those who were sexually active aged 18 to 49 years. A sample size network of 10 000 was selected and symptomatic proportion was set at 10%. Treatment was given to those who were symptomatic. Three

control strategies were evaluated: screening without contact tracing, screening plus expedited partner therapy, and screening plus partner testing with re-testing and targeted testing for higher risk population (>1 partners). Successfully traced partners would receive treatment without a laboratory test to confirm infection (ie, over-treatment) or treatment after a positive result was returned.

A cost-effectiveness model was constructed, with the outputs of the dynamic transmission model to estimate the cost, benefits, and resulting quality adjusted life year (QALY) gained from each scenario (Table 1). In universal screening (scenarios A), coverage of 10% and 30% of the sexually active population per year was applied, without consideration of number of partners or symptoms. In targeted testing with follow-up testing at 3 months, 6 months, or 1 year (Scenarios B and C), two fractions of symptomatic patients who sought treatment was applied: a worst-case scenario of 10% and a more realistic scenario at 30%. In targeted testing for a higher risk population (>1 partners) [Scenarios D and E], all scenarios were implemented in a network with 10% symptomatic population with a similar proportion of screened patients as universal screening. Each scenario was run with a range of partner trace efficiency of 2%, 10%, 20%, and 40%.

Results

A total of 520 individuals (40% males) [mean age, 36.8 years] participated in the discrete choice experiments. 66% of them had a bachelor's degree or higher. The choice of chlamydia testing was most influenced by cost, followed by speed of results, delivery of results, extra testing for STI, availability of testing, and location of testing. Those aged >35 years and women had greater dislike for paying HK$600 than their counterparts. Heterogeneity related to the appointment time, whether extra tests were offered, and opt out was not explained by age, sex, born in Hong Kong, or having >1 sexual partner. The most important factor in chlamydia management was staff attitude, followed by cost, who to consult, availability

TABLE 1. Different scenarios used in analysis

Scenario	Universal screening	Targeted screening only	Targeted screening plus partner tracing		Fraction symptomatic, %	Follow-up period, mo	% of population screened in a year	Partner trace efficiency, %
			Treatment to all	Testing to all				
Universal screening								
Ai	X	-	-	-	10	-	~10	-
Aii	X	-	-	-	10	-	~30	-
Targeted testing and follow-up testing of patients seeking treatment								
Bi	-	X	-	-	10	3	-	-
Bii	-	X	-	-	-	6	-	-
Biii	-	X	-	-	-	12	-	-
Biv	-	-	X	-	-	3	-	40
Bv	-	-	-	X	-	-	-	
Ci	-	X	-	-	30	-	-	-
Cii	-	-	X	-	-	-	-	40
Ciii	-	-	-	X	-	-	-	
Targeted testing of population with >1 partners								
Di	-	X	-	-	10	-	~10	-
Dii	-	-	X	-	-	-	-	2
Diii	-	-	X	-	-	-	-	10
Div	-	-	X	-	-	-	-	20
Dv	-	-	X	-	-	-	-	40
Ei	-	-	-	X	-	-	-	2
Eii	-	-	-	X	-	-	-	10
Eiii	-	-	-	X	-	-	-	20
Eiv	-	-	-	X	-	-	-	40

of patient-delivered partner therapy, travel time, and treatment location. There was significant variation in preferences for cost, availability of patient-delivered partner therapy, travel time, who to consult, and staff attitude.

The average chlamydia prevalence for universal screening (10% coverage) and targeted testing of higher-risk population at equilibrium was 3.24%±0.31% and 3.35%±0.38%, respectively, and after intervention was 2.75%±0.30% and 2.35%±0.21%, respectively. This could be further reduced to 1.48%±0.13% with 40% contact tracing efficiency (Fig). We did not observe a significant change in the overall prevalence from scenarios targeting follow-up screening simulations. The most cost-effective scenarios were those with intervention focusing on the higher-risk population with contact tracing (Table 2). Reasonable-to-good cost-effectiveness were obtained in targeted testing scenarios t with follow-up screening to patients seeking attention. There was extensive over-treatment (ie, treatment of un-infected traced individuals) in scenarios. Scenarios with testing preceded treatment for traced individuals almost eliminated the over-treatment problem but were less cost-effective owing to the high testing costs.

Discussion

The most influential factor in improving uptake of chlamydia testing is cost. Currently, Hong Kong residents can be tested for free at social hygiene clinics, but only 14% reported they had ever tested for chlamydia. To improve chlamydia testing uptake in Hong Kong, wider availability of free testing in other primary care settings is needed. The most influential factor in improving uptake of chlamydia management is staff attitude. Self-stigma and anticipated provider stigma are major barriers for people accessing testing services.[3] Availability of patient-delivered partner therapy may increase uptake of management, which is not available in Hong Kong. Further explorations may be warranted.

Universal screening is not cost-effective

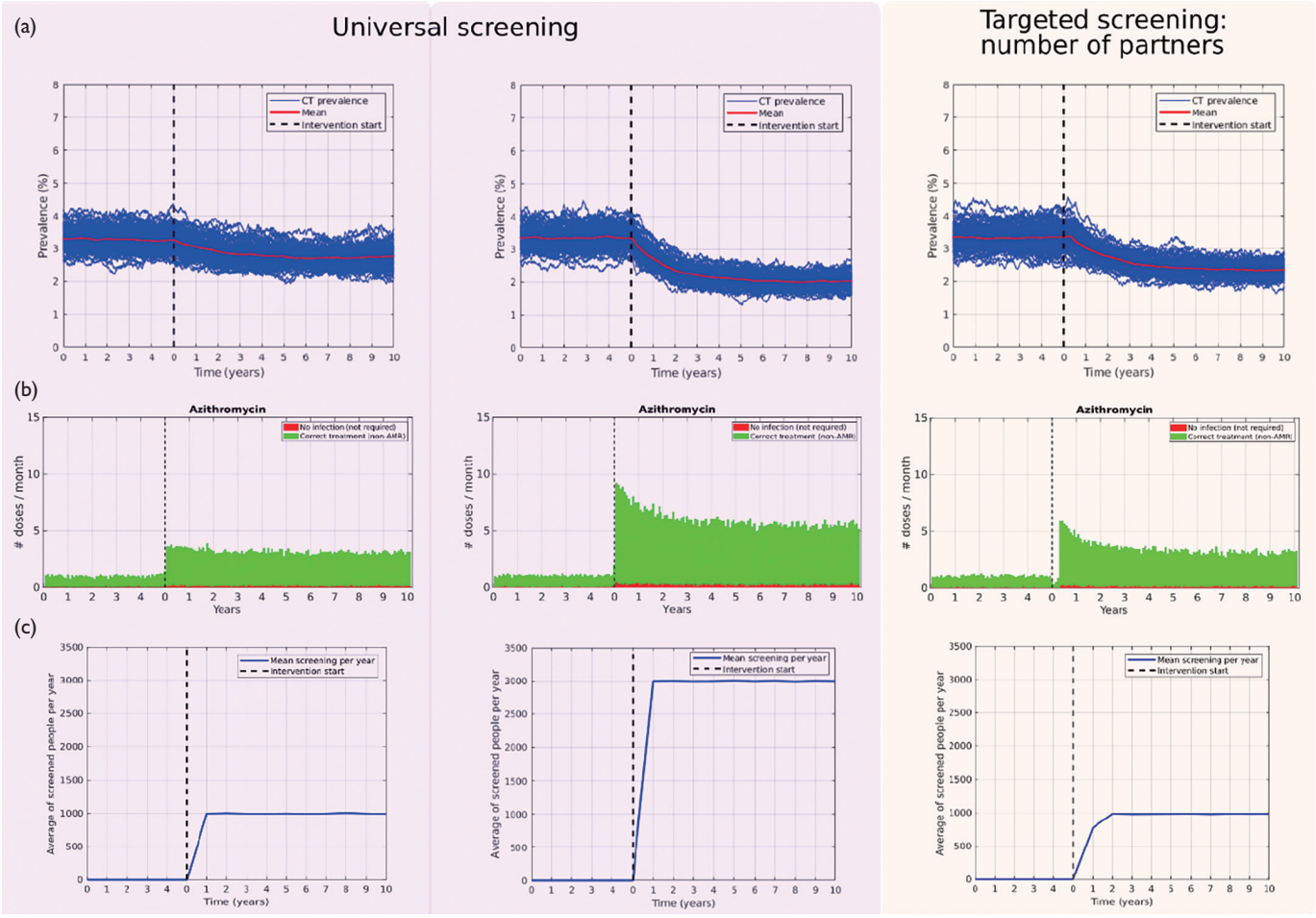

FIG. Comparison between universal screening covering 10% and 30% of the population per year and targeted screening of higher risk population in terms of (a) the prevalence results over 100 simulations and the mean percentage of prevalence, (b) the number of doses provided per month for those with or without chlamydia infection, and (c) the average number of people screened per day.

TABLE 2. Cost-effectiveness analysis of different scenarios*

Scenario	Newly incurred direct cost/quality adjusted life year gain, HK$		Net cost/quality adjusted life year gain, HK$	
	Year 1	Year 10	Year 1	Year 10
Universal screening				
Ai	512 499	343 590	487 348	318 438
Aii	596 685	423 059	571 533	397 907
Targeted testing and follow-up testing of patients seeking treatment				
Bi	-110 978	54 265	-136 130	29 113
Bii	55 798	67 573	30 646	42 421
Biii	-1978	19 254	-27 130	-5898
Biv	40 943	-87 493	15 791	-112 645
Bv	90 293	219 212	65 142	194 060
Ci	115 551	125 699	90 399	100 547
Cii	79 901	100 692	54 749	75 540
Ciii	354 610	255 767	329 458	230 615
Targeted testing of population with >1 partners				
Di	362 043	185 584	336 891	160 432
Dii	45 335	49 740	20 183	24 588
Diii	29 622	31 921	4470	6769
Div	28 511	30 398	3359	5246
Dv	28 845	30 612	3693	5460
Ei	356 063	200 862	330 911	175 710
Eii	521 497	322 297	496 345	297 145
Eiii	593 423	422 323	568 271	397 171
Eiv	634 844	540 549	609 692	515 397

* Direct costs include clinic attendance, treatment, tracing, and testing costs, whereas net costs additionally include the reduction in costs owing to averted complications

compared with targeted testing with strengthened patient management and contact tracing. However, this could be challenging as people may not accurately disclose their sexual activity or under-report the number of sexual partners. At-risk individuals with multiple partners should be targeted to improve efficiency and cost-effectiveness of any chlamydia testing programmes. Measures to decrease stigma such as normalising sexual health checks and routine sexual health history taking by health providers are critical for improving the uptake of chlamydia testing among higher-risk individuals.

Contact tracing of partners of infected individuals is important for STI control. Testing plus contact tracing performs better in reducing the prevalence with increased effectiveness, compared with testing only. Prompt evaluation and treatment of sexual contacts are important to interrupt transmission, prevent reinfection, and prevent sequelae. However, contact tracing is challenging in Hong Kong owing to the stigma associated with STIs, feeling uncomfortable disclosing an STI diagnosis to sexual partners, and fear of relationship breakup or violence.[5] In addition, expedited partner therapy does not significantly affect overall chlamydia prevalence and may cause overtreatment. Partners should ideally be tested before treatment to avoid overtreatment and antimicrobial resistance.

Conclusion

Discrete choice experiments and comprehensive modelling evaluation are used to identify patient preferences and optimal strategies to control chlamydia in Hong Kong. Cost and staff attitude are the most important factors to test and treat chlamydia, respectively. Targeted screening with contact tracing is the most cost-effective strategy to reduce chlamydia prevalence in Hong Kong.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#18171282). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

Disclosure

The results of this research have been previously published in:

1. Ong JJ, Fairley CK, Hocking JS, et al. Preferences for chlamydia testing and management in Hong Kong: a discrete choice experiment. Sex Transm Infect 2022;98:408-13.
2. Montes-Olivas S, Homer M, Turner K, et al. Evaluating the impact and cost-effectiveness of chlamydia management strategies in Hong Kong: a modeling study. Front Public Health 2022;10:932096.

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Surveillance of environmental contamination by antibiotics and antibiotic-resistant pathogens: abridged secondary publication

K Fukuda *, T Lam, H Tun, JSM Peiris, BJ Cowling, T Zhang

KEY MESSAGES

1. A great diversity of antibiotic resistance genes (ARGs) including mobile colistin resistance genes are identified from sewage of Queen Mary Hospital and influent and effluent of Sandy Bay Preliminary Treatment Works.
2. A large amount of multi-drug-resistant *Escherichia coli* and *Klebsiella pneumoniae* isolates are obtained from samples.
3. Abundance of several ARGs is associated with water temperature. The use of fluoroquinolone in hospitals is positively associated with the abundance of fluoroquinolone resistance genes.
4. The resistome profile of the sewage from a hospital site has higher similarity to that of the influent at Sandy Bay Preliminary Treatment Works.

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The emergence and rapid spread of antibiotic-resistant bacteria is a major threat to global health. Antibiotic resistance is often attributed to the overuse and misuse of antibiotics in humans and animals so that bacteria acquire resistance against antibiotics through natural mutations or lateral transfer of resistance genes. This highlights the problem of mobility of antibiotic resistance genes (ARGs) from bacteria to bacteria, between bacteria and the environment, and between humans, animals, and the environment. Determining the source and dissemination pathways of ARGs is challenging and requires extensive and multi-sector collaborative efforts. Such knowledge is important for developing effective control and prevention strategies.

There have been studies investigating the emergence of antimicrobial resistance (AMR) among patients in hospitals.[1,2] Sewage surveillance to monitor AMR and other pathogens such as SARS-CoV-2 is useful to assess environmental contamination by pathogens.[3,4] In Hong Kong, such sewage surveillance for hospital AMR has not been fully assessed. Such work may provide insight into emergence of AMR in the human sector and dissemination to environments.

We conducted a 1-year longitudinal surveillance of AMR in wastewater discharged from the Queen Mary Hospital (QMH) and in the influent and effluent from the nearby wastewater treatment plant (Sandy Bay Preliminary Treatment Works, SBPTW) between February 2019 and January 2020. The study used multiple approaches to characterise the antibiotic-resistant bacteria, resistance genes, and residues in the wastewater samples. Both culture and metagenomic methods were used to delineate the bacterial-resistant profiles in phenotypic and genotypic levels. The study aimed to determine the dynamics and diversity of bacteria population, antibiotic resistance, residue, and usage in these locations over time, so as to determine the associations and factors of AMR emergence and potential dissemination.

Metagenomic sequencing identified a wide spectrum (all known classes) of antibiotic-resistant genes. The top three commonest ARGs were multidrug resistance genes, beta lactam resistance genes, and aminoglycoside resistance genes among samples from QMH, and multidrug resistance genes, aminoglycoside resistance genes, and beta-lactam resistance genes among samples from SBPTW. Notably, a wide range of mobile colistin resistant genes 1 to 10 were found.

Culture experiments revealed that the most dominant two Enterobacteriaceae species were *Escherichia coli* and *Klebsiella pneumoniae*. Antibiotic susceptibility tests showed that more than half of Enterobacteriaceae isolates were resistant to at least one antimicrobial, among which *K pneumoniae* isolates were more resistant to antimicrobials than *E coli* isolates. Notably, a significant higher number of multidrug-resistant isolates of *E coli* and *K pneumoniae* were found in wastewater samples from QMH than from SBPTW. There were temporal variations on the drug resistance profiles for *E coli* and *K pneumoniae* isolates in terms of sites and dates.

Liquid chromatography–tandem mass spectrometry analysis showed that samples from the clinical blocks of QMH contained higher levels of antimicrobial residues (amoxicillin, ampicillin, cefuroxime, metronidazole, sulfamethoxazole, trimethoprim, and vancomycin) than those from the SBPTW. The overall antibiotic usage in QMH was associated with sewage resistance profiles in some sampling sites. For instance, the abundance of fluoroquinolone resistance genes was associated with the fluoroquinolone weekly usage; the residue of sulphonamide antibiotics was strongly associated with the sulphonamide ARGs. Abundance of a number of ARGs was positively associated with the temperature of water samples.

In conclusion, there was a great diversity of multidrug-resistant Enterobacteriaceae and different types of ARGs (such as mobile colistin resistant genes 1 to 10) in the sewage of QMH and SBPTW. There appeared to be a contamination pathway from QMH sewage to the environment, as relatively higher resistome similarity was noted between a discharge site in QMH and the influent in SBPTW. Long-term surveillance of antibiotic use through hospital sewage and treatment plant samples can be used to track the resistance emergence and spread.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#17161342). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

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Novel dentotropic antimicrobial peptide to prevent dental caries: abridged secondary publication

CH Chu *, ML Mei, WKK Wu

KEY MESSAGES

1. GA-KR12 can be successfully synthesised with high purity (98.98%).
2. GA-KR12 is a biocompatible stable peptide with antimicrobial and remineralising properties.
3. GA-KR12 can significantly reduce the *Streptococcus mutans* mono-species biofilm and inhibit its metabolism and growth.
4. GA-KR12 prevents the demineralisation of tooth hard tissue and enhance the remineralisation of artificial caries on enamel and dentine.
5. Grafting a mineralising molecule and an antimicrobial peptide to develop a novel peptide against caries is a viable strategy.

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Introduction

Dental caries is perhaps the most prevalent chronic disease worldwide; most carious teeth are left untreated.[1] Controlling oral microbial biofilms and maintaining tooth minerals are equally important to prevent/control caries. Antimicrobial peptides are the first line of defence against infection of multicellular organisms and a potential therapeutic strategy for managing oral diseases.[2] Gallic acid is a component for inducing and accelerating mineralisation owing to its pyrogallol moiety.[3] KR12 is an ideal template peptide derived from LL-37.[4] KR12 is small size and has low toxicity and antimicrobial properties against cariogenic species. We developed a novel dentotropic antimicrobial peptide using gallic acid and KR12 and evaluated its antimicrobial effect against cariogenic biofilm and its remineralisation effect on enamel and dentine caries.

Methods

The novel dentotropic antimicrobial peptide was created by grafting gallic acid as a mineralising domain to the N-terminal of peptide KR12 as an antimicrobial domain (Fig 1). The peptide GA-KR12 was synthesised using standard fluorenylmethoxycarbonyl synthesis via standard solid-phase peptide synthesis. After the synthesis, high-performance liquid chromatography and mass spectrum and circular dichroism spectroscopy were

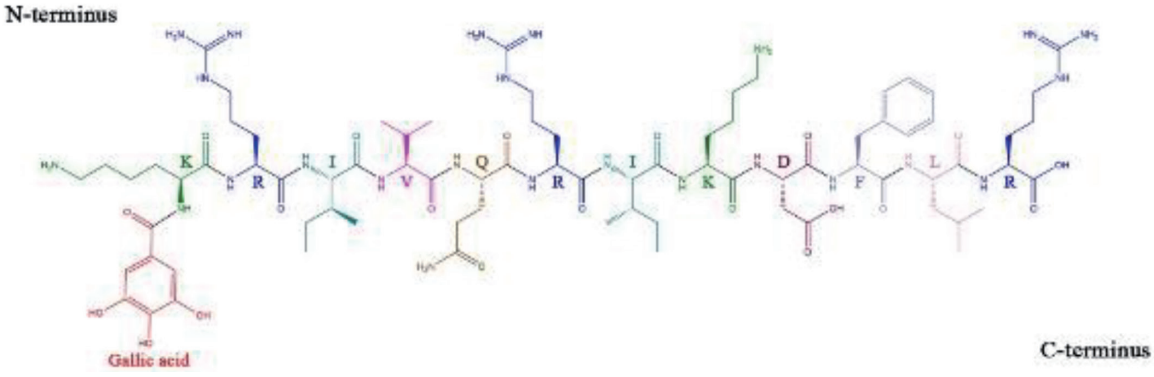

FIG 1. The structure of GA-KR12

used to evaluate the purity, molecular weight, and secondary structure of GA-KR12. Human gingival fibroblasts were used to evaluate the cytotoxicity of GA-KR12 by mitochondrial dehydrogenase activity assay. Six cariogenic species were used to evaluate the antimicrobial properties of GA-KR12 by minimum inhibitory concentration and minimum bactericidal/fungicidal concentration. The morphology of cariogenic species was analysed by transmission electron microscope. The architecture, viability, and growth kinetics of the cariogenic biofilm (*Streptococcus mutans*) were determined by scanning electron microscopy (SEM), confocal laser scanning microscopy, and culture colony-forming units (CFUs), respectively. The mineral loss, calcium-to-phosphorus ratio, surface morphology, and crystal characteristics of the enamel surface were determined by micro-computed tomography, energy dispersive spectroscopy, SEM, and X-ray diffraction, respectively. The mineral loss, changes in chemical structure, surface morphology, and crystal characteristics of the dentine surface were determined by micro-computed tomography, Fourier transform infrared, SEM, and X-ray diffraction, respectively.

TABLE. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) / minimum fungicidal concentration (MFC) of GA-KR12, KR12, and chlorhexidine against cariogenic species

Cariogenic species	GA-KR12	KR12	Chlorhexidine
Streptococcus mutans			
MIC, μM	160	320	1.25
MBC, μM	320	1280	10
Streptococcus sobrinus			
MIC, μM	320	No activity	5
MBC, μM	1280	No activity	20
Lactobacillus acidophilus			
MIC, μM	320	40	2.50
MBC, μM	1280	160	40
Lactobacillus rhamnosus			
MIC, μM	320	No activity	2.50
MBC, μM	1280	No activity	20
Actinomyces naeslundii			
MIC, μM	160	320	0.16
MBC, μM	640	1280	0.32
Candida albicans			
MIC, μM	10	10	0.16
MFC, μM	20	20	0.32

Results

GA-KR12 was successfully synthesised with high purity (98.98%). The molecular weight of GA-KR12 was 1724.04. GA-KR12 was biocompatible to human gingival fibroblast. The minimum inhibitory concentration and minimum bactericidal concentration / minimum fungicidal concentration against the tested species were 10 to 320 μM and 20 to 1280 μM, respectively (Table). GA-KR12 induced remarkable morphological defects in the tested species.

SEM showed confluent growth of *S mutans* in the water group but not in the GA-KR12-treated group (Fig 2). The live-to-dead ratios and log CFUs of the GA-KR12-treated group were lower than those of the water group. The mineral loss of the GA-KR12-treated group was lower than that of the water group. The calcium-to-phosphorus molar ratios of the GA-KR12-treated group were higher than that of the water group. A uniformly remineralised prismatic pattern on enamel blocks was observed in the GA-KR12-treated group. The hydroxyapatite on the enamel surface in the GA-KR12-treated group was better crystallised than that in the water group.

The surface of the dentine blocks *S mutans* partially covered the GA-KR12-treated group with a damaged cell structure (Fig 3). The live-to-dead ratios and log CFUs of the GA-KR12-treated group were lower than those of the water group. The mineral loss and amide I-to-hydrogen ratio of the GA-KR12-treated group were lower than that of the water group. SEM images showed that the GA-KR12-treated group had less exposed dentine collagen fibres than the water group.

Discussion

GA-KR12 is a biocompatible and stable peptide with antimicrobial and remineralising properties. It inhibits the growth of cariogenic species and promotes the remineralisation of caries on enamel and dentine. This is the first study to graft gallic acid to an antimicrobial peptide to achieve a dentotropic antimicrobial peptide. Gallic acid with a pyrogallol moiety has the same mechanism as tunicate does to induce mineralisation.[3] KR12 is an ideal template peptide because of its small size, low toxicity, and antimicrobial properties against cariogenic species.[4]

In the present study, GA-KR12 was synthesised by standard solid-phase peptide synthesis. GA-KR12 had similar percentages of the α-helical and β-sheet structures with those obtained in a previous study for KR12.[5] GA-KR12 was biocompatible to human gingival fibroblast and safe for dental use. GA-KR12 treatment changed the morphology of the bacteria and fungi cells. Because of the interaction between the negatively charged cell membrane and the

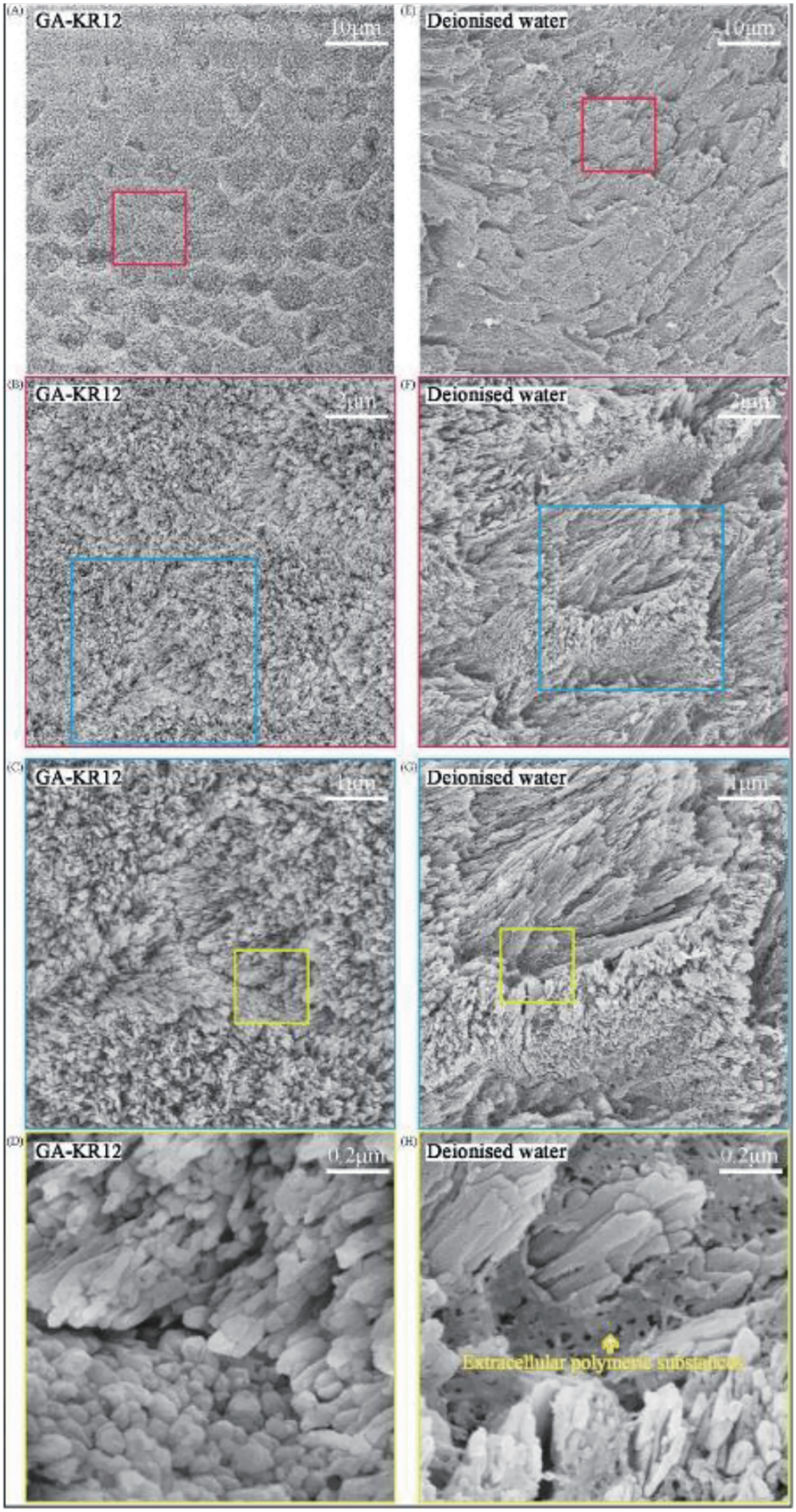

FIG 2. Scanning electron microscopy images of enamel surface morphology of the GA-KR12 and the deionised water groups (1000×, 5000×, 10 000×, and 50 000×)

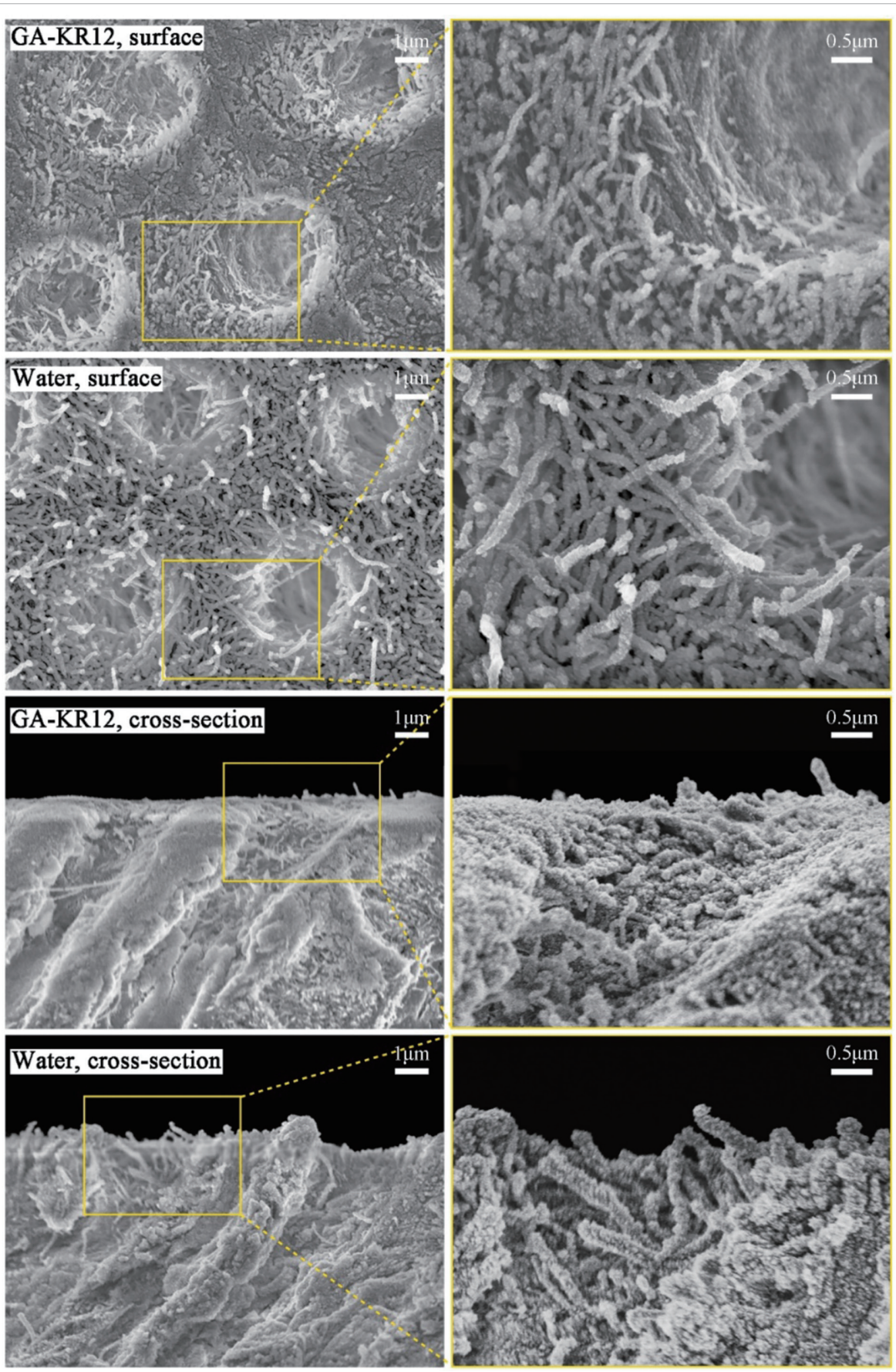

FIG 3. Scanning electron microscopy images of dentine morphology in the GA-KR12 and the deionised water groups (7000× and 20 000×)

positively charged peptide, the cells showed an irregular cell shape and an abnormal membrane curvature. Subsequently, the cell membrane was disrupted by the inserting of the peptides, which caused cytoplasmic content to be leaked. Furthermore, GA-KR12 could significantly reduce the *S mutans* mono-species biofilm and inhibit its metabolism and growth. SEM images indicated that the affluence of the *S mutans* biofilm was less in the GA-KR12-treated group. In addition, some *S mutans* cells lost their regular cell shape.

Hard tissues of the tooth include enamel and dentine. The mineral structures of enamel and dentine are different. In the present study, the remineralising effect of GA-KR12 to enamel and dentine caries was evaluated separately using an *S mutans* biofilm–remineralisation cycling model, which combined biological and chemical factors to provide periodic pH alternation and a microbiological environment for bacterial impact. GA-KR12 effectively promoted the remineralisation of both enamel and dentine caries and the formation of an extra-fibrillar mineral. The probable mechanisms could be that GA-KR12 prevent the degradation of collagen scaffold and acidic dissolution of mineral crystal by inhibition of *S mutans* biofilm. Moreover, the pyrogallol group of GA-KR12 can attract calcium ions from the remineralising solution to promote the remineralisation of the caries.

Conclusion

GA-KR12 is a biocompatible stable peptide with antimicrobial and mineralising properties. GA-KR12 can significantly reduce the *S mutans* mono-species biofilm and inhibit its metabolism and growth. GA-KR12 can prevent the demineralisation of tooth hard tissue and enhance the remineralisation of artificial caries on enamel and dentine. Grafting a mineralising molecule and an antimicrobial peptide to develop a novel peptide against caries is a viable strategy.

Funding

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Disclosure

The results of this research have been previously published in:

1. Niu JY, Yin IX, Wu WKK, Li QL, Mei ML, Chu CH. Efficacy of the dual-action GA-KR12 peptide for remineralising enamel caries: an in vitro study. Clin Oral Investig 2022;26:2441-51.
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Suppression of type I and type II interferon production and signalling by Epstein-Barr virus BGLF2 protein: abridged secondary publication

DY Jin *, KS Yuen, MG Botelho

KEY MESSAGES

1. The Epstein-Barr virus (EBV) has to circumvent the production and action of interferons (IFNs) in order to replicate and maintain a high copy number of its DNA genome in infected cells.
2. EBV effectively suppresses induction of IFN-stimulated genes.
3. BGLF2 tegument protein is a potent suppressor of JAK-STAT signalling.
4. BGLF2 recruits SHP1 phosphatase to STAT1 and targets STAT2 for degradation.
5. BGLF2-defective EBV activates IFN signalling more robustly.
6. Our findings have important implications in understanding EBV-associated diseases and developing antivirals or vaccines.

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Introduction

Host innate immunity recognises pathogen-associated molecular patterns of Epstein-Barr virus (EBV) such as its DNA to counteract viral infection, replication, and reactivation. As countermeasures, EBV subverts innate immunity using some of its lytic proteins such as BGLF5, which targets TLR9 for degradation during lytic replication.[1] EBV also encodes a deubiquitinase and a late lytic tegument protein named BPLF1, which deubiquitinates and inactivates multiple signal transducers in innate immune signalling.[2,3] The outcome of EBV infection is dictated by the interplay between EBV and innate immunity, but the mechanistic details of this interplay are incompletely understood. Particularly, additional EBV-encoded suppressors of interferon (IFN) signalling remain to be identified and characterised.

JAK-STAT signalling activated upon binding of IFNs to their respective receptors mediates the downstream effects of all three types of IFNs.[4] For type I and type III IFNs, a ternary complex comprising pSTAT1, pSTAT2, and IRF9 binds to IFN-stimulated response elements (ISREs) in the promoter region of IFN-stimulated genes (ISGs) to activate transcription. For type II IFN, γ-activated factor is a dimeric p-STAT1, which recognises γ-activated sequence in the promoter region of a subset of unique ISGs. Protein tyrosine phosphatases such as SHP1 are negative regulators of JAK-STAT signalling. EBV is thought to subvert JAK-STAT signalling by use of multiple countermeasures. Identification and characterisation of novel EBV-encoded IFN antagonists may elucidate how EBV engages cellular negative regulators and cripples cellular activators to modulate critical events in JAK-STAT signalling.

Methods

We expressed BGLF2 in transfected lymphoid and epithelial cells to characterise its suppressive activity on type I and type II IFN production and signalling. We dissected its action points in the pathways of IFN production and signalling as well as the underlying molecular mechanism. Importantly, we used a BGLF2-deficient recombinant virus to analyse the relevance and biological significance of BGLF2-induced innate immunosuppression in EBV infection and pathogenesis.

Results

Inhibition of type I, type II, and type III IFN signalling by BGLF2

The negative regulatory effect of EBV BGLF2 on IFN signalling was validated. HEK293 cells were used for this experiment owing to its high transfection efficiency and full competence of IFN signalling. BGLF2 inhibited ISRE-Luc activity in a dose-dependent fashion. When levels of ISG15 and OAS1 mRNAs were quantified, BGLF2 was found to exert an inhibitory effect on expression of these two ISGs in the presence of IFN-β. Moreover, BGLF2 dampened IFN-β-stimulated expression of ISG15

protein. Enforced expression of BGLF2 in HEK293 cells resulted in the suppression of IFN-γ-dependent γ-activated sequence–Luc activity. In agreement with this, IFN-γ-activated expression of IP10 transcript was mitigated by BGLF2. A pronounced suppressive effect of BGLF2 on IFN-λ1-induced activation of ISRE-Luc activity, ISG15 mRNA expression, and OAS1 mRNA expression was observed.

Inhibition of STAT1 phosphorylation by BGLF2 through recruitment of SHP1 phosphatase

JAK-STAT signalling is intricately regulated by tyrosine phosphatases.[5] To determine whether tyrosine phosphatases were affected by BGLF2, BGLF2-overexpressing HEK293 cells were either treated or left untreated with Na_3VO_4, which inhibits a wide spectrum of tyrosine phosphatases. Interestingly, treatment with Na_3VO_4 prevented the reduction of p-STAT1 level in the presence of IFN-β and BGLF2. A series of RNA interference experiments were carried out to pinpoint which tyrosine phosphatase was involved. SHP1, which is known to dephosphorylate key transducers of JAK-STAT signalling, was a prime candidate. SHP1 was depleted in HEK293 cells by siRNA. The requirement of SHP1 tyrosine phosphatase for suppression of STAT1 phosphorylation and activation by BGLF2 was verified. Total SHP1 protein levels were not affected by BGLF2, but both SHP1 and BGLF2 were found to associate with STAT1. These findings are in general agreement with the concept that BGLF2 recruits SHP1 to dampen STAT1 signalling.

EBV infection and reactivation by BGLF2 through suppression of type I IFN signalling

The GFP-marked M81 strain of EBV enables identification of infected cells as GFP-positive cells. This facilitates investigation of how IFN-β and BGLF2 affect EBV infection. When HEK293 cells were pre-treated with IFN-β, EBV infectivity diminished, compared with the untreated group. Overexpression of BGLF2 led to reversal of this phenotype. This was generally in keeping with results obtained in flow cytometric analysis of GFP-positive cells. The EBV genome copy number was also diminished upon treatment with IFN-β. Pre-expression of BGLF2 prior to IFN-β treatment reversed the fall in the genome copy number. Furthermore, the expression of EBV lytic genes including BLLF1/gp350, BMRF1, and BRLF1/Rta was suppressed by IFN-β in M81-infected HEK293 cells. This suppression was relieved when BGLF2 was expressed. Hence, BGLF2 counteracts IFN-β in the inhibition of EBV infection.

Discussion

BGLF2 was identified to be a suppressor of JAK-STAT signalling through multiple mechanisms, independent of the modulatory effect on JNK, p38, or NF-κB. BGLF2 binds to STAT1, STAT2, and cullin 1. It recruits tyrosine phosphatase SHP1 to STAT1 and leads to STAT1 dephosphorylation and inactivation. It also recruits cullin 1 to STAT2 and results in STAT2 ubiquitination and proteolysis. Expression of lytic genes is less pronounced in a BGLF2-deficient EBV, concurrent with a more robust induction of ISG expression. Thus, BGLF2 serves as a suppressor of JAK-STAT signalling and a facilitator of EBV infection.

Conclusions of our study and those of another study[5] are generally consistent regarding the suppression of IFN signalling and promotion of EBV reactivation by BGLF2. We demonstrated the impact of BGLF2 on primary infection of EBV. Importantly, we constructed BGLF2-deficient EBV and provided the first evidence for its increased activity in IFN-β signalling.

Type III IFNs exhibit strong antiviral property against herpes simplex virus infection in vivo, but the roles of IFN-1 in EBV infection remain elusive. We demonstrated the inhibitory effect of EBV and its BGLF2 protein on type I and type III IFN signalling. Whether type III IFNs are induced by EBV and influential in EBV primary infection and reactivation warrant further investigations.

BGLF2 is a multifunctional tegument protein. BGLF2 exerts differential effects on STAT1 and STAT2. Particularly, BGLF2 does not target STAT1 for degradation or dephosphorylate STAT2. Further studies are warranted to elucidate the specificity of the effect of BGLF2 on STAT1 and STAT2 by differences in binding domains, nature of conformational changes, and/or partner selection. The SH2 domain present in all STATs for recognition, and binding to pTyr in other JAKs or STATs is highly conserved. In contrast, coiled-coil domain, transcriptional activation domain and other regions in STATs are more divergent. Further studies are needed to determine whether their binding with BGLF2 might be responsible for the differential effects. The conformational changes induced by the binding of BGLF2 with STAT1 and STAT2 may account for the differential effects. We revealed that SHP1 and cullin 1 were key mediators of the effect of BGLF2 on STAT1 and STAT2, respectively. Although no interaction between BGLF2 and SHP2 was detected, further investigations are required to clarify whether additional protein tyrosine phosphatases including SHP2 and additional cullin-type E3 ubiquitin ligases are involved in BGLF2-depenent suppression of STAT1 and STAT2.

Other cellular and viral proteins have been shown to recruit other E3 ubiquitin ligases (UBR4, PDLIM2, and Fbw7) to augment STAT2 ubiquitination and degradation. Further studies are

warranted to determine the mechanisms by which different E3s cooperate with each other to mediate STAT2 ubiquitination and degradation in different physiological and pathological settings. Cullin 1 is only one of the key components in the SCF complex, which represents a large family of cullin-RING E3 ubiquitin ligases. Our finding provides new support to the notion that SCF complex might be critical in the degradation of STAT2. Experimental validation of the role of SKP1 and cullin 1 in STAT2 ubiquitination and degradation is warranted.

BGLF2 is highly conserved among herpesviruses. Homologs of EBV BGLF2 include herpes simplex virus 1 UL16, murine gammaherpesvirus 68 ORF33, cytomegalovirus UL94, varicella zoster virus ORF44, and Kaposi's sarcoma-associated herpesvirus ORF33. Some of these homologs are also known to be capable of inducing cell cycle arrest. It is important to investigate if they can also recruit SHP1 and cullin 1 to suppress JAK-STAT signalling.

Funding

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Disclosure

The results of this research have been previously published in:

1. Jangra S, Bharti A, Lui WY, et al. Suppression of JAK-STAT signaling by Epstein-Barr virus tegument protein BGLF2 through recruitment of SHP1 phosphatase and promotion of STAT2 degradation. J Virol 2021;95:e0102721.

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Maternal antibody against influenza neuraminidase in newborns: abridged secondary publication

RAPM Perera *, SSS Chiu, RSL Au Yeung, JSM Peiris

KEY MESSAGES

1. Infants whose mothers had a history of vaccination have a significantly higher maternal antibodies (MatNAb) titres to both group 1 and group 2 influenza viruses.
2. Infants whose mothers had a history of vaccination have significantly lower influenza infection than those whose mothers did not.
3. Lower birth weight is associated with lower MatNAb titres for N1 responses but not for N2 responses. When the birth weight is <2 kg, the MatNAb titres tend to be lower. Infected infants have significantly lower titres of N1 seasonal influenza.
4. The MatNAb titres can reduce the relative risk of influenza infection and is correlated with reduction in infection than haemagglutinin inhibition titres. When the MatNAb titre is ≥160, >50% relative risk reduction from infection is achieved.
5. Influenza vaccination in pregnant mothers can boost MatNAb titres in infants and reduce the risk of influenza infection. Therefore, inclusion of neuraminidase in influenza vaccines is beneficial.

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Influenza is a major public health concern worldwide, particularly in densely populated Hong Kong. In 2008, one million cases of influenza occurred in children aged <5 years.[1] Influenza immunity is acquired in an age- and exposure-related manners. Infants and young children are an important link in the transmission chain of influenza in communities and families. They are considered drivers of yearly epidemics. Infants aged <6 months do not possess an effective endogenous immune defence against influenza, and influenza vaccines are not recommended for infants aged <6 months.

Maternal antibodies (MatNAb) are mainly immunoglobulin (Ig) G, which is transferred through the placenta to protect newborns against influenza. The transfer of IgG is mediated by neonatal Fc receptor expressed on syncytiotrophoblast cells, depending on maternal titre of IgG, gestational age, placental integrity, IgG subclass, and nature of antigen.[2] Maternal immunisation can elevate the total IgG.

For infants, protection against influenza is provided by IgA from breast milk, but both IgA and IgG do not cross the intestinal epithelium in sufficient amounts. The major host protection in lung against influenza is IgG derived from serum. Thus, it is important to evaluate protection effects of serum antibodies transferred from placenta to infants.[3]

Antibodies to the influenza hemagglutinin play a role against specific strains. There is increasing evidence on the more important protective role of anti-neuraminidase antibodies.[4] The function of neuraminidase is to release budding virions from cells to facilitate spread to new cells. When neuraminidase is blocked by antibodies, the virions remain aggregated in a manner that hinder binding to cell receptors of new cells. Thus, virions are not able to spread and initiate subsequent rounds of infection. Consequently, the amplification and continuation of the infection process comes to a standstill. Therefore, antibodies against neuraminidase do not enable sterilising immunity but protection or resistance against infection and reduction of disease severity.[5] Thus, neuraminidase is a useful vaccine protective antigen. Moreover, the high conservation of viral neuraminidase makes the antibodies that bind to it largely cross-protective against novel strains. We aim to characterise the MatNAb and determine its correlation with protection against influenza in newborns.

Our results indicated that geometric mean titres for MatNAb responses against N1 and N2 seasonal influenza in infants were significantly higher when mothers had a history of vaccination, compared with those who did not. MatNAb responses were associated with seasonal MatNAb titre, infant birth weight, and mothers smoking status, but not with infant sex. There was a trend

that birth weight of <2 kg was associated with lower neuraminidase responses for seasonal N1 but not for seasonal N2. MatNAb titres were significantly lower in infants infected by influenza within the first 2 months after birth. Most infections in infants were H3N2 infections. The cross-reactive MatNAb titres against unexposed highly pathogenic influenza viruses such as H5N1 were lower compared with seasonal MatNAb titres. The neuraminidase titre was not correlated with birth weight.

In conclusion, infants of vaccinated mothers have higher MatNAb titres to both group 1 and group 2 influenza viruses. Lower birth weight is associated with lower MatNAb titres for N1 responses but not for N2 responses. When the birth weight is <2 kg, the MatNAb titres tend to be lower. Infected infants have significantly lower titres of N1 seasonal influenza but not of N2 seasonal influenza. The MatNAb titres tend to reduce the relative risk of influenza infection and is correlated with reduction in infection than haemagglutinin inhibition titres. Influenza vaccination in pregnant mothers can help boost the MatNAb titres in infants and reduce the risk of influenza infection. Therefore, inclusion of neuraminidase in influenza vaccines is beneficial.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#05163486). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

Acknowledgements

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Recurrent miscarriage and risk of obstetric and perinatal complications in subsequent pregnancy: abridged secondary publication

TC Li *, BHK Yip, X Chen

KEY MESSAGES

1. Chinese women with a history of recurrent miscarriage have an increased risk of several obstetric and perinatal complications in the subsequent pregnancy.
2. Women with a history of recurrent miscarriage should be offered specialist obstetric care from the start of pregnancy, with emphasis on strategies to manage the increased risk of preterm birth, small for gestational age, and perinatal death.

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Introduction

Miscarriage is estimated to occur in 11% to 20% of all clinically recognised pregnancies before the 24th week of gestation. The European Society of Human Reproduction and Embryology recommends to define recurrent miscarriage (RM) as two or more pregnancies loss.[1] Many women with a history of RM may go on to carry a pregnancy beyond 24 weeks, but it remains controversial whether these pregnancies are at higher risk in later stages of pregnancy. There is a need for evidence-based counselling for obstetric and perinatal outcomes in the subsequent pregnancy for Hong Kong women with a history of RM.

The Clinical Data Analysis and Reporting System (CDARS) in Hong Kong provides clinical information for management decision, clinical audit, research, and data analysis. This study aims to examine if any adverse obstetric and perinatal outcomes are associated with a history of RM among women in Hong Kong.

Methods

Medical records of all women with a history of RM and singleton pregnancy who were admitted between January 2000 and December 2019 at the Department of Obstetrics and Gynaecology, the Prince of Wales Hospital, The Chinese University of Hong Kong were retrieved from CDARS. All women underwent maternal and paternal karyotyping, basal hormone profiling, prothrombotic screening and antiphospholipid antibody test, thyroid function and thyroid antibodies tests, and ultrasonography. All other women without a history of RM during the same period were included for comparison. Women with multiple pregnancies were excluded.

Maternal characteristics extracted included age, marital status, type of pregnancy (natural or assisted conception), gestational age at booking. Gestational age was estimated based on the first day of the last menstrual period in the women with regular cycle, but ultrasound estimate was preferred if the date was uncertain or had a discrepancy of >7 days. Obstetric outcomes in the subsequent pregnancy included gestational hypertensive disorders, antepartum haemorrhage, gestational diabetes, preterm labour, and the mode of delivery. Perinatal outcomes included gestational age at delivery, small for gestational age, large for gestational age, infant sex, Apgar scores at 1 and 5 min, admission rate to the neonatal unit, perinatal death, and genital anomalies. Diseases were coded using the International Classification of Diseases, 9th Revision, Clinical Modification. Data validation by reviewing individual electronic medical records demonstrated high coding accuracy for diagnosis.

Analyses were performed using the SPSS (Windows version 25; IBM Corp, Armonk [NY], US). Comparisons between groups were made using the Student's *t* test, ANOVA, or non-parametric test for continuous variables and Chi-squared test or Fisher's exact test for categorical variables. Univariable logistic regression analyses and multivariable stepwise logistic regression analyses were performed, adjusting for baseline differences between groups. A P value of <0.05 was considered statistically significant.

Results

Of 111 124 women with singleton pregnancy included for analysis, 3112 (2.8%) had a history of two or more miscarriages and 108 012 (97.2%) did not (Table 1). Of the 3112 women with a history of

RM, 697 (22.4%) had primary RM and 2415 (77.6%) had secondary RM.

Women with a history RM had significantly increased odds of gestational hypertension (odds ratio [OR]=1.28) and Caesarean section (OR=1.47). After adjusting for maternal age, type of pregnancy, and gestational age at booking, only Caesarean section remained significant (adjusted OR=1.55, Table 2).

Women with a history of RM had higher rates of preterm delivery (OR=1.67), small for gestational age (OR=1.64), and perinatal death from all causes (OR=1.48), even after adjusting for confounders (adjusted OR=1.72, 1.70, and 1.52, respectively) [Table 3].

TABLE 1. Characteristics of participants

Characteristic	Recurrent miscarriage (n=3112)*	Control (n=108 012)*	P value
Maternal age, y			<0.001
<20	21 (0.7)	5562 (5.1)	-
20-29	691 (22.2)	37804 (35.0)	-
30-39	1979 (63.2)	57246 (53.0)	-
>40	421 (13.5)	7400 (6.9)	-
Body mass index, kg/m^2	22.3±3.8	22.9±4.2	0.058
Type of pregnancy			<0.001
Natural conception	2552 (82.0)	96932 (90.0)	-
Assisted conception	560 (18.0)	11080 (10.0)	-
Gestational age at booking, wk			<0.001
<12	1408 (45.2)	44284 (41.0)	-
12-20	1556 (50.0)	56166 (52.0)	-
>20	148 (4.8)	7562 (7.0)	-

* Data are presented as mean ± standard deviation or No. (%) of participants

Discussion

Women with a history of RM are at higher risk of several adverse obstetric and perinatal outcomes including preterm labour, Caesarean section, small

TABLE 2. Obstetric outcomes

Obstetric outcome	No. (%) of participants		Odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
	Recurrent miscarriage (n=3112)	Control (n=108 012)		
Gestational hypertension	154 (4.9)	4221 (3.9)	1.28 (1.09-1.51)*	1.14 (0.98-1.28)
Preeclampsia	24 (0.8)	688 (0.6)	1.21 (0.81-1.82)	1.17 (0.77-1.93)
Eclampsia	4 (0.1)	121 (0.1)	1.15 (0.42-3.1)	1.10 (0.35-3.77)
Antepartum haemorrhage	101 (3.2)	3212 (3.0)	1.09 (0.90-1.34)	1.04 (0.72-1.43)
Gestational diabetes	156 (5.0)	4921 (4.6)	1.12 (0.98-1.31)	1.08 (0.92-1.41)
Operative vaginal delivery	291 (9.4)	10092 (9.3)	1.00 (0.89-1.13)	1.00 (0.98-1.14)
Caesarean section	827 (26.6)	21312 (19.7)	1.47 (1.36-1.60)*	1.55 (1.32-1.77)*

* P<0.05

TABLE 3. Perinatal outcomes

Perinatal outcome	No. (%) of participants		Odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
	Recurrent miscarriage (n=3112)	Comparison group (n=108 012)		
Infant sex			1.11 (1.04-1.20)	-
Female	1608 (51.7)	52926 (49.0)	-	-
Male	1504 (48.3)	55086 (51.0)	-	-
Preterm birth	252 (8.1)	5400 (5.0)	1.67 (1.47-1.91)*	1.72 (1.50-1.99)*
Small for gestational age	150 (4.8)	3229 (3.0)	1.64 (1.39-1.94)*	1.70 (1.41-1.98)*
Large for gestational age	109 (3.5)	3886 (3.6)	0.97 (0.80-1.18)	1.01 (0.79-1.24)
Apgar score <7 at 1 min	89 (2.9)	3080 (2.9)	1.00 (0.81-1.24)	1.02 (0.80-1.25)
Apgar score <7 at 5 min	35 (1.1)	1100 (1.0)	1.11 (0.79-1.56)	1.01 (0.70-1.49)
Admission to neonatal unit	404 (13.0)	14022 (13.0)	1.00 (0.90-1.11)	1.01 (0.83-1.20)
Perinatal death	31 (1.0)	728 (0.7)	1.48 (1.03-2.12)*	1.52 (1.11-2.32)*
Congenital anomalies	28 (0.9)	746 (0.7)	1.30 (0.89-1.90)	1.21 (0.71-2.19)

* P<0.05

for gestational age, and perinatal death. More intensive antenatal monitoring is required for this group of women.

In a large epidemiological study of pregnancy outcomes between women with a previous miscarriage and women with a previous successful pregnancy, women with primary miscarriage were at significant higher risk of pre-eclampsia, antepartum haemorrhage, and low birth weight in the subsequent pregnancy.[2]

A history of RM has been reported to associate with preterm delivery, perinatal death, and delivery by Caesarean section, but the sample size of the study was small. However, in a study of 42 women, no significant difference in the risk of developing growth restriction, delivery by Caesarean section, or perinatal death was reported between women with unexplained RM and controls.[3] Another study of women with RM did not adjust for the effects of confounders.[4]

Although we demonstrated a significantly increased risk of several obstetric and perinatal adverse outcomes in women with a history of RM, RM can be caused by a heterogeneous group of conditions, some of which can be associated with an increased risk of pregnancy complications, and thus there is a potential bias owing to these confounders. Women with unexplained RM is most suitable for examining pregnancy outcomes, because the confounding effects of other pathologies is minimised.

There are several limitations to the present study. The Prince of Wales Hospital is a tertiary referral hospital, and the control group may be slightly skewed towards higher pregnancy risk. Study population was mainly Chinese and may not be compared with other ethnic populations. Owing to the retrospective nature of the study, some clinical parameters including detailed paternal information may be missing.

Conclusions

Chinese women with a history of two or more miscarriages have an increased risk of several obstetric and perinatal complications.

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