SUPPLEMENT 3

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Research Dissemination Reports

醫療衞生研究基金

研究成果報告

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Health and Medical Research Fund

Research Dissemination Reports

INFECTIOUS DISEASES

CHINESE MEDICINE

IMPLEMENTATION SCIENCE

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 12 dissemination reports of projects related to advanced technology, non-communicable diseases, primary healthcare, infectious diseases, Chinese medicine, and implementation science. In particular, research findings of three projects may provide insights to enhance clinical practices and help inform health policy formulation in Hong Kong.

Osteoporosis increases the risk of fragility fracture. Hip fractures are projected to increase significantly in Hong Kong and Asia in the coming decades. Fracture prediction models are available but are mainly developed using data from Western populations. Li et al[1] developed and validated sex- and ethnicity-specific machine learning models to predict 10- and 15-year hip fracture risks using data from over 128 000 electronic medical records. The prediction models were developed without bone mineral density as a potential predictor, owing to the limited availability of dual-energy X-ray absorptiometry in Hong Kong. The prediction models achieved an area under the curve of >0.8 after validation in independent cohorts and may be clinically useful and generalisable to the public.

Family members who care for individuals affected by dementia often experience adverse effects, and effective interventions are needed to alleviate this burden. Chou et al[2] conducted a prospective, assessor-blinded, randomised controlled study to evaluate the effects of five different intervention components among 250 Chinese adult caregivers. Over 12 months, a mindfulness-based intervention component contributed to a reduction in anxiety and depression symptoms, an increase in psychological well-being, and an increase in functional social support, as well as an increase in dementia management strategies of active management, mindfulness attention awareness, and satisfaction with the support group. The other intervention components provided benefit in fewer domains overall. Results suggested that intervention programmes for distressed family caregivers of individuals with dementia should include components of mindfulness-based intervention and support group, which are cost-effective and can improve coping mechanisms and foster a supportive environment for their well-being.

Preschool children around the world are affected by caries. The occlusal surface of primary molars is highly susceptible to caries. Yiu et al[3] determined the relative effectiveness and costs of sodium fluoride varnish and glass ionomer sealants in preventing occlusal caries in primary molars of over 400 preschool children from 16 kindergartens in Hong Kong. Three-monthly application of sodium fluoride varnish and a single application of glass ionomer sealant were equally effective in preventing occlusal caries in primary molars over 24 months.

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Machine learning models for hip fracture prediction using electronic medical records: abridged secondary publication

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KEY MESSAGES

1. Ethnicity- and sex-specific hip fracture prediction models were developed using machine learning algorithms and electronic medical records. The performance of the prediction models was validated in independent cohorts, achieving the area under the curve values of >0.8. The prediction models may be clinically useful and generalisable to the public.
2. The prediction models were developed without using bone mineral density as a potential predictor, owing to the limited availability of dual-energy X-ray absorptiometry in Hong Kong.

Introduction

Osteoporosis is characterised by low bone mass and deterioration in bone strength and microarchitecture, increasing the risk of fragility fracture. In 2050, the number of hip fractures in Asia is expected to reach 2.56 million.[1] In Hong Kong, an estimated 27 468 hip fractures will occur in that year, costing approximately HK$1.9 billion annually.[1]

Fracture prediction models, such as the Fracture Risk Assessment Tool, are mainly developed using data from Western populations. Among the Hong Kong population, fracture prediction based on ethnicity-specific clinical risk factors and femoral neck bone mineral density (BMD) T-score outperforms that of the Fracture Risk Assessment Tool.[2] Dual-energy X-ray absorptiometry is the gold standard in diagnosing osteoporosis and predicting fracture. However, its availability is considerably low. In Hong Kong public hospitals, the median waiting time for a scan is 9 months.[3] Therefore, it is important to develop a fracture risk prediction tool without BMD data. This study aimed to develop and validate sex- and ethnicity-specific machine learning models to predict the 10- and 15-year hip fracture risks, based on demographic, diagnostic, and prescription data from electronic medical records.

Methods

Anonymised medical records were retrieved from the Clinical Data Analysis and Reporting System of the Hospital Authority. As of 31 December 2005 (index date), approximately 740 000 public healthcare service users aged ≥60 years had admission records between 1 January and 31 December 2005. Around one-third of them were randomly selected as the derivation cohort; they were followed up until hip fracture, death, or study end dates (31 December 2015 and 31 December 2020 for 10- and 15-year risk prediction, respectively), whichever occurred earlier. The derivation cohort was stratified by sex, and each sex-specific sub-cohort was randomly divided into an internal training (80%) and internal testing (20%) dataset. Performance of the prediction models was further assessed in an external validation cohort comprising participants aged ≥60 years from the Hong Kong Osteoporosis Study,[4] which comprised 9449 community-dwelling Southern Chinese participants. The external validation cohort did not overlap with the derivation cohort. In the supplementary analysis, individuals who had been lost to follow-up or died before study end dates were excluded.

Potential predictors included age, number of hospitalisations, and diagnosis and drug prescription records within 1 year of the index date. The presence or absence of each diagnosis code and drug class was recorded. Initially, there were 396 potential predictors (162 diagnosis variables and 232 drug prescription variables). Variables with zero or near-zero variance (≤0.1% prevalence) were excluded.

A multistep model selection procedure for logistic regression (LR) was applied to the development dataset (ie, 80% of the derivation cohort). This approach to finding the model that penalised variable addition involved minimising the metric of the Akaike information criterion (ie, including all predictors at the start, then performing stepwise selection by LR, which added and dropped predictors to identify a model with the lowest Akaike information criterion).

TABLE 1a. Characteristics of female participants.

Variable	10-year risk*						15-year risk*					
	Whole sample			Excluding those lost to follow-up			Whole sample			Excluding those lost to follow-up		
	Derivation cohort		External validation cohort (n=2520)	Derivation cohort		External validation cohort (n=2038)	Derivation cohort		External validation cohort (n=2520)	Derivation cohort		External validation cohort (n=1762)
	Training cohort (n=103515)	Testing cohort (n=25878)		Training cohort (n=73541)	Testing cohort (n=18385)		Training cohort (n=103515)	Testing cohort (n=25878)		Training cohort (n=60659)	Testing cohort (n=15164)	
Hip fracture cases	7568 (7.3)	1892 (7.3)	145 (5.8)‡	7568 (10.3)	1892 (10.3)	145 (7.1)‡	10743 (10.4)	2685 (10.4)	211 (8.4)‡	10743 (17.7)	2685 (17.7)	211 (12.0)‡
Age, y	73 (60-114)	73 (60-114)	71 (60-100)‡	71 (60-106)	71 (60-103)	69 (60-95)‡	73 (60-114)	73 (60-107)	71 (60-100)‡	70 (60-106)	70 (60-100)	68 (60-95)‡
No. of hospital admissions	0 (0-22)	0 (0-21)	0 (0-9)‡	0 (0-21)	0 (0-21)	0 (0-9)‡	0 (0-21)	0 (0-22)	0 (0-9)‡	0 (0-13)	0 (0-21)	0 (0-9)‡
Diagnosis (within 1 year)												
Chronic obstructive pulmonary disease and allied conditions	1557 (1.5)	400 (1.5)	21 (0.8)	574 (0.8)	130 (0.7)	10 (0.5)	1573 (1.5)	384 (1.5)	21 (0.8)‡	408 (0.7)	105 (0.7)	7 (0.4)
Any cancer												
Malignant neoplasm of lip, oral cavity, and pharynx	42 (0.0)	5 (0.0)	0 (0.0)	15 (0.0)	4 (0.0)	0 (0.0)	35 (0.0)	12 (0.0)	0 (0.0)	9 (0.0)	3 (0.0)	0 (0.0)
Malignant neoplasm of digestive organs and peritoneum	401 (0.4)	96 (0.4)	7 (0.3)	140 (0.2)	40 (0.2)	2 (0.1)	402 (0.4)	95 (0.4)	7 (0.3)	131 (0.2)	22 (0.1)	2 (0.1)
Malignant neoplasm of respiratory and intrathoracic organs	157 (0.2)	34 (0.1)	4 (0.2)	22 (0.0)	3 (0.0)	0 (0.0)	143 (0.1)	48 (0.2)	4 (0.2)	18 (0.0)	5 (0.0)	0 (0.0)
Malignant neoplasm of bone, connective tissue, skin, and breast	257 (0.2)	65 (0.3)	8 (0.3)	135 (0.2)	36 (0.2)	6 (0.3)	257 (0.2)	65 (0.3)	8 (0.3)	111 (0.2)	28 (0.2)	6 (0.3)
Malignant neoplasm of genitourinary organs	228 (0.2)	60 (0.2)	2 (0.1)	98 (0.1)	30 (0.2)	2 (0.1)	241 (0.2)	47 (0.2)	2 (0.1)	75 (0.1)	24 (0.2)	2 (0.1)
Malignant neoplasm of other and unspecified sites	316 (0.3)	76 (0.3)	3 (0.1)	55 (0.1)	20 (0.1)	1 (0.0)	322 (0.3)	70 (0.3)	3 (0.1)	49 (0.1)	12 (0.1)	1 (0.1)
Malignant neoplasm of lymphatic and haematopoietic tissue	94 (0.1)	17 (0.1)	6 (0.2)‡	18 (0.0)	5 (0.0)	3 (0.1)‡	94 (0.1)	17 (0.1)	6 (0.2)‡	13 (0.0)	6 (0.0)	2 (0.1)
Cardiovascular disease												
Chronic rheumatic heart disease	193 (0.2)	31 (0.1)†	1 (0.0)	64 (0.1)	23 (0.1)	1 (0.0)	189 (0.2)	35 (0.1)	1 (0.0)	49 (0.1)	14 (0.1)	1 (0.1)
Hypertensive disease	4319 (4.2)	1098 (4.2)	87 (3.5)	1937 (2.6)	497 (2.7)	48 (2.4)	4328 (4.2)	1089 (4.2)	87 (3.5)	1462 (2.4)	301 (2.0)†	38 (2.2)
Ischaemic heart disease	1898 (1.8)	451 (1.7)	31 (1.2)‡	780 (1.1)	230 (1.3)†	17 (0.8)	1884 (1.8)	465 (1.8)	31 (1.2)‡	604 (1.0)	139 (0.9)	13 (0.7)
Diseases of pulmonary circulation	57 (0.1)	7 (0.0)	1 (0.0)	18 (0.0)	3 (0.0)	0 (0.0)	52 (0.1)	12 (0.0)	1 (0.0)	18 (0.0)	2 (0.0)	0 (0.0)
Other forms of heart disease	3102 (3.0)	777 (3.0)	40 (1.6)‡	952 (1.3)	232 (1.3)	15 (0.7)‡	3091 (3.0)	788 (3.0)	40 (1.6)‡	674 (1.1)	193 (1.3)	11 (0.6)
Cerebrovascular disease	2261 (2.2)	576 (2.2)	35 (1.4)‡	829 (1.1)	217 (1.2)	12 (0.6)‡	2254 (2.2)	583 (2.3)	35 (1.4)‡	608 (1.0)	157 (1.0)	7 (0.4)‡
Diseases of arteries, arterioles, and capillaries	366 (0.4)	95 (0.4)	11 (0.4)	130 (0.2)	25 (0.1)	4 (0.2)	371 (0.4)	90 (0.3)	11 (0.4)	86 (0.1)	30 (0.2)	2 (0.1)
Diseases of veins and lymphatics, and other diseases of circulatory system	767 (0.7)	163 (0.6)	18 (0.7)	383 (0.5)	97 (0.5)	13 (0.6)	750 (0.7)	180 (0.7)	18 (0.7)	308 (0.5)	71 (0.5)	10 (0.6)
Psychotic conditions, including dementias and alcohol-induced mental disorders	1565 (1.5)	367 (1.4)	28 (1.1)	374 (0.5)	101 (0.5)	4 (0.2)	1547 (1.5)	385 (1.5)	28 (1.1)	272 (0.4)	53 (0.3)	4 (0.2)
Rheumatism, excluding the back	438 (0.4)	113 (0.4)	14 (0.6)	296 (0.4)	86 (0.5)	11 (0.5)	436 (0.4)	115 (0.4)	14 (0.6)	254 (0.4)	69 (0.5)	10 (0.6)
Nephritis, nephrotic syndrome, and nephrosis	934 (0.9)	212 (0.8)	15 (0.6)	170 (0.2)	44 (0.2)	2 (0.1)	917 (0.9)	229 (0.9)	15 (0.6)	119 (0.2)	38 (0.3)	1 (0.1)
Diseases of endocrine glands, including diabetes mellitus, disorders of pituitary and parathyroid glands, and ovarian dysfunction	3230 (3.1)	796 (3.1)	57 (2.3)‡	1290 (1.8)	353 (1.9)	25 (1.2)	3218 (3.1)	808 (3.1)	57 (2.3)‡	919 (1.5)	242 (1.6)	17 (1.0)
Previous fracture												
Fracture of skull	46 (0.0)	9 (0.0)	2 (0.1)	23 (0.0)	9 (0.0)	2 (0.1)	43 (0.0)	12 (0.0)	2 (0.1)	22 (0.0)	2 (0.0)	2 (0.1)
Fracture of neck and trunk	395 (0.4)	86 (0.3)	14 (0.6)	188 (0.3)	54 (0.3)	6 (0.3)	372 (0.4)	109 (0.4)	14 (0.6)	141 (0.2)	40 (0.3)	5 (0.3)
Fracture of upper limb	879 (0.8)	201 (0.8)	22 (0.9)	496 (0.7)	123 (0.7)	15 (0.7)	882 (0.9)	198 (0.8)	22 (0.9)	413 (0.7)	91 (0.6)	13 (0.7)
Fracture of lower limb	1236 (1.2)	324 (1.3)	47 (1.9)‡	599 (0.8)	144 (0.8)	23 (1.1)	1229 (1.2)	331 (1.3)	47 (1.9)‡	486 (0.8)	107 (0.7)	17 (1.0)
Drug prescription (within 1 year)												
Any antidepressants (BNF 4.3)	5019 (4.8)	1236 (4.8)	88 (3.5)‡	2856 (3.9)	764 (4.2)	62 (3.0)‡	5015 (4.8)	1240 (4.8)	88 (3.5)‡	2270 (3.7)	559 (3.7)	56 (3.2)
Drugs used in rheumatic diseases and gout (BNF 10.1)	19080 (18.4)	4719 (18.2)	336 (13.3)‡	13516 (18.4)	3380 (18.4)	270 (13.2)‡	19050 (18.4)	4749 (18.4)	336 (13.3)‡	11090 (18.3)	2878 (19.0)	235 (13.3)‡
Corticosteroids												
Respiratory (BNF 3.2)	2488 (2.4)	646 (2.5)	40 (1.6)‡	1294 (1.8)	281 (1.5)†	27 (1.3)	2562 (2.5)	572 (2.2)	40 (1.6)‡	976 (1.6)	220 (1.5)	22 (1.2)
Endocrine (BNF 6.3)	3845 (3.7)	962 (3.7)	51 (2.0)‡	1875 (2.5)	484 (2.6)	25 (1.2)‡	3887 (3.8)	920 (3.6)	51 (2.0)‡	1462 (2.4)	355 (2.3)	20 (1.1)‡
Topical (BNF 13.4)	14975 (14.5)	3785 (14.6)	212 (8.4)‡	10165 (13.8)	2454 (13.3)	175 (8.6)‡	15031 (14.5)	3729 (14.4)	212 (8.4)‡	8167 (13.5)	2061 (13.6)	145 (8.2)‡

Abbreviation: BNF=British National Formulary

* Data are presented as median (range) or No. (%) of participants.

† P<0.05 between training and testing cohorts

‡ P<0.05 between derivation and external validation cohorts

TABLE 1b. Characteristics of male participants.

Variable	10-year risk*						15-year risk*					
	Whole sample			Excluding those lost to follow-up			Whole sample			Excluding those lost to follow-up		
	Derivation cohort		External validation cohort (n=1277)	Derivation cohort		External validation cohort (n=1008)	Derivation cohort		External validation cohort (n=1277)	Derivation cohort		External validation cohort (n=834)
	Training cohort (n=88 483)	Testing cohort (n=22 120)		Training cohort (n=55 301)	Testing cohort (n=13 824)		Training cohort (n=88 483)	Testing cohort (n=22 120)		Training cohort (n=41 877)	Testing cohort (n=10 468)	
Hip fracture cases	3301 (3.7)	825 (3.7)	36 (2.8)	3301 (6.0)	825 (6.0)	36 (3.6)‡	4791 (5.4)	1197 (5.4)	58 (4.5)	4791 (11.4)	1197 (11.4)	58 (7.0)‡
Age, y	71 (60-107)	71 (60-105)	70 (60-96)‡	69 (60-104)	69 (60-101)	68 (60-96)	71 (60-107)	71 (60-105)	70 (60-96)‡	68 (60-104)	68 (60-103)	68 (60-96)
No. of hospital admissions	0 (0-42)	0 (0-24)	0 (0-8)‡	0 (0-42)	0 (0-18)	0 (0-4)‡	0 (0-30)	0 (0-42)	0 (0-8)‡	0 (0-18)	0 (0-21)	0 (0-3)‡
Diagnosis (within 1 year)												
Chronic obstructive pulmonary disease and allied conditions	2927 (3.3)	729 (3.3)	29 (2.3)‡	716 (1.3)	174 (1.3)	8 (0.8)	2912 (3.3)	744 (3.4)	29 (2.3)‡	482 (1.2)	109 (1.0)	5 (0.6)
Any cancer												
Malignant neoplasm of lip, oral cavity, and pharynx	89 (0.1)	22 (0.1)	1 (0.1)	31 (0.1)	4 (0.0)	1 (0.1)	82 (0.1)	29 (0.1)	1 (0.1)	20 (0.0)	6 (0.1)	0 (0.0)
Malignant neoplasm of digestive organs and peritoneum	700 (0.8)	180 (0.8)	5 (0.4)	186 (0.3)	46 (0.3)	3 (0.3)	708 (0.8)	172 (0.8)	5 (0.4)	130 (0.3)	39 (0.4)	2 (0.2)
Malignant neoplasm of respiratory and intrathoracic organs	320 (0.4)	88 (0.4)	1 (0.1)	62 (0.1)	15 (0.1)	0 (0.0)	326 (0.4)	82 (0.4)	1 (0.1)	45 (0.1)	13 (0.1)	0 (0.0)
Malignant neoplasm of bone, connective tissue, skin, and breast	44 (0.0)	14 (0.1)	3 (0.2)‡	21 (0.0)	6 (0.0)	0 (0.0)‡	45 (0.1)	13 (0.1)	3 (0.2)‡	15 (0.0)	5 (0.0)	3 (0.4)‡
Malignant neoplasm of genitourinary organs	613 (0.7)	169 (0.8)	3 (0.2)	217 (0.4)	66 (0.5)	2 (0.2)	601 (0.7)	181 (0.8)†	3 (0.2)	160 (0.4)	31 (0.3)	1 (0.1)
Malignant neoplasm of other and unspecified sites	449 (0.5)	113 (0.5)	1 (0.1)‡	69 (0.1)	18 (0.1)	1 (0.1)	437 (0.5)	125 (0.6)	1 (0.1)	60 (0.1)	14 (0.1)	0 (0.0)
Malignant neoplasm of lymphatic and haematopoietic tissue	95 (0.1)	40 (0.2)	1 (0.1)	26 (0.0)	9 (0.1)	0 (0.0)	106 (0.1)	29 (0.1)	1 (0.1)	19 (0.0)	5 (0.0)	0 (0.0)
Cardiovascular disease												
Chronic rheumatic heart disease	92 (0.1)	32 (0.1)	1 (0.1)	42 (0.1)	11 (0.1)	1 (0.1)	99 (0.1)	25 (0.1)	1 (0.1)	22 (0.1)	10 (0.1)	0 (0.0)
Hypertensive disease	3714 (4.2)	915 (4.1)	31 (2.4)‡	1439 (2.6)	374 (2.7)	15 (1.5)‡	3669 (4.1)	960 (4.3)	31 (2.4)‡	1002 (2.4)	251 (2.4)	8 (1.0)‡
Ischaemic heart disease	2248 (2.5)	557 (2.5)	23 (1.8)	990 (1.8)	240 (1.7)	7 (0.7)‡	2234 (2.5)	571 (2.6)	23 (1.8)	663 (1.6)	175 (1.7)	5 (0.6)‡
Diseases of pulmonary circulation	64 (0.1)	20 (0.1)	1 (0.1)	11 (0.0)	7 (0.1)	1 (0.1)	67 (0.1)	17 (0.1)	1 (0.1)	8 (0.0)	5 (0.0)	1 (0.1)
Other forms of heart disease	2532 (2.9)	659 (3.0)	29 (2.3)	756 (1.4)	211 (1.5)	9 (0.9)	2558 (2.9)	633 (2.9)	29 (2.3)	506 (1.2)	126 (1.2)	6 (0.7)
Cerebrovascular disease	2426 (2.7)	596 (2.7)	21 (1.6)‡	850 (1.5)	196 (1.4)	10 (1.0)	2408 (2.7)	614 (2.8)	21 (1.6)‡	572 (1.4)	139 (1.3)	8 (1.0)
Diseases of arteries, arterioles, and capillaries	461 (0.5)	113 (0.5)	6 (0.5)	151 (0.3)	27 (0.2)	2 (0.2)	455 (0.5)	119 (0.5)	6 (0.5)	91 (0.2)	26 (0.2)	0 (0.0)
Diseases of veins and lymphatics, and other diseases of circulatory system	825 (0.9)	200 (0.9)	8 (0.6)	380 (0.7)	108 (0.8)	6 (0.6)	819 (0.9)	206 (0.9)	8 (0.6)	300 (0.7)	79 (0.8)	4 (0.5)
Psychotic conditions, including dementias and alcohol-induced mental disorders	922 (1.0)	230 (1.0)	15 (1.2)	158 (0.3)	43 (0.3)	1 (0.1)	929 (1.0)	223 (1.0)	15 (1.2)	115 (0.3)	35 (0.3)	1 (0.1)
Rheumatism, excluding the back	307 (0.3)	76 (0.3)	4 (0.3)	183 (0.3)	46 (0.3)	3 (0.3)	303 (0.3)	80 (0.4)	4 (0.3)	135 (0.3)	35 (0.3)	3 (0.4)
Nephritis, nephrotic syndrome, and nephrosis	967 (1.1)	237 (1.1)	7 (0.5)	170 (0.3)	61 (0.4)†	3 (0.3)	954 (1.1)	250 (1.1)	7 (0.5)	135 (0.3)	30 (0.3)	2 (0.2)
Diseases of endocrine glands, including diabetes mellitus, disorders of pituitary and parathyroid glands, and ovarian dysfunction	2680 (3.0)	694 (3.1)	15 (1.2)‡	967 (1.7)	229 (1.7)	7 (0.7)‡	2730 (3.1)	644 (2.9)	15 (1.2)‡	618 (1.5)	165 (1.6)	5 (0.6)‡
Previous fracture												
Fracture of skull	53 (0.1)	10 (0.0)	0 (0.0)	20 (0.0)	6 (0.0)	0 (0.0)	49 (0.1)	14 (0.1)	0 (0.0)	20 (0.0)	4 (0.0)	0 (0.0)
Fracture of neck and trunk	139 (0.2)	26 (0.1)	0 (0.0)	68 (0.1)	18 (0.1)	0 (0.0)	137 (0.2)	28 (0.1)	0 (0.0)	51 (0.1)	11 (0.1)	0 (0.0)
Fracture of upper limb	251 (0.3)	58 (0.3)	2 (0.2)	117 (0.2)	42 (0.3)	2 (0.2)	243 (0.3)	66 (0.3)	2 (0.2)	99 (0.2)	26 (0.2)	0 (0.0)
Fracture of lower limb	496 (0.6)	116 (0.5)	3 (0.2)	209 (0.4)	59 (0.4)	2 (0.2)	483 (0.5)	129 (0.6)	3 (0.2)	185 (0.4)	33 (0.3)	1 (0.1)
Drug prescription (within 1 year)												
Any antidepressants (BNF 4.3)	2236 (2.5)	532 (2.4)	29 (2.3)	1117 (2.0)	248 (1.8)	15 (1.5)	2190 (2.5)	578 (2.6)	29 (2.3)	795 (1.9)	183 (1.7)	12 (1.4)
Drugs used in rheumatic diseases and gout (BNF 10.1)	16443 (18.6)	4213 (19.0)	161 (12.6)‡	9908 (17.9)	2511 (18.2)	124 (12.3)‡	16481 (18.6)	4175 (18.9)	161 (12.6)‡	7494 (17.9)	1841 (17.6)	94 (11.3)‡
Corticosteroids												
Respiratory (BNF 3.2)	3918 (4.4)	990 (4.5)	31 (2.4)‡	1346 (2.4)	307 (2.2)	13 (1.3)‡	3961 (4.5)	947 (4.3)	31 (2.4)‡	852 (2.0)	228 (2.2)	7 (0.8)‡
Endocrine (BNF 6.3)	5144 (5.8)	1335 (6.0)	36 (2.8)‡	1863 (3.4)	461 (3.3)	19 (1.9)‡	5198 (5.9)	1281 (5.8)	36 (2.8)‡	1314 (3.1)	307 (2.9)	12 (1.4)‡
Topical (BNF 13.4)	12363 (14.0)	3090 (14.0)	135 (10.6)‡	7175 (13.0)	1834 (13.3)	95 (9.4)‡	12341 (13.9)	3112 (14.1)	135 (10.6)‡	5347 (12.8)	1318 (12.6)	75 (9.0)‡

Abbreviation: BNF=British National Formulary

* Data are presented as median (range) or No. (%) of participants.

† P<0.05 between training and testing cohorts

‡ P<0.05 between derivation and external validation cohorts

TABLE 2a. Performance of hip fracture risk prediction models for women.

Performance	Stepwise selection by logistic regression		Gradient boosting machine		Random forest		Extreme gradient boosting		Neural networks with a single hidden layer		Naïve Bayes	
	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk
Training cohort												
Area under the curve (95% confidence interval)	0.716 (0.71-0.721)	0.669 (0.664-0.674)	0.687 (0.682-0.693)	0.643 (0.638-0.648)	0.997 (0.996-0.997)	0.996 (0.996-0.996)	0.675 (0.669-0.681)	0.631 (0.626-0.636)	0.691 (0.685-0.697)	0.66 (0.655-0.665)	0.521 (0.514-0.528)	0.519 (0.513-0.525)
Testing cohort												
Area under the curve (95% confidence interval)	0.705 (0.694-0.716)	0.652 (0.641-0.662)	0.677 (0.665-0.689)	0.627 (0.616-0.637)	0.65 (0.638-0.661)	0.593 (0.582-0.603)	0.663 (0.651-0.675)	0.61 (0.599-0.621)	0.67 (0.658-0.683)	0.623 (0.612-0.634)	0.5 (0.5-0.5)	0.478 (0.469-0.487)
Sensitivity	0.724	0.687	0.715	0.694	0.11	0.102	0.721	0.591	0.687	0.587	0.244	0.202
Specificity	0.59	0.542	0.55	0.51	0.929	0.924	0.526	0.581	0.586	0.59	0.817	0.844
Positive predictive value	0.122	0.148	0.111	0.141	0.109	0.135	0.107	0.14	0.116	0.142	0.095	0.131
Negative predictive value	0.964	0.937	0.961	0.935	0.93	0.899	0.96	0.925	0.96	0.925	0.932	0.901
F1	0.209	0.244	0.193	0.234	0.109	0.116	0.187	0.227	0.198	0.229	0.137	0.159
Accuracy	0.6	0.557	0.562	0.53	0.869	0.839	0.54	0.582	0.594	0.59	0.775	0.778
Error	0.4	0.443	0.438	0.471	0.131	0.161	0.46	0.418	0.406	0.41	0.225	0.222
External validation cohort												
Area under the curve (95% confidence interval)	0.769 (0.734-0.803)	0.724 (0.691-0.757)	0.757 (0.718-0.795)	0.702 (0.667-0.738)	0.669 (0.629-0.708)	0.607 (0.569-0.645)	0.745 (0.705-0.784)	0.691 (0.653-0.728)	0.713 (0.67-0.757)	0.685 (0.651-0.72)	0.5 (0.5-0.5)	0.456 (0.419-0.494)
Sensitivity	0.724	0.697	0.772	0.758	0.241	0.242	0.807	0.697	0.717	0.645	0.414	0.341
Specificity	0.699	0.661	0.621	0.573	0.852	0.849	0.581	0.615	0.648	0.64	0.726	0.743
Positive predictive value	0.128	0.158	0.111	0.14	0.091	0.128	0.105	0.142	0.111	0.141	0.085	0.108
Negative predictive value	0.976	0.96	0.978	0.963	0.949	0.924	0.98	0.957	0.974	0.952	0.953	0.925
F1	0.218	0.258	0.194	0.236	0.132	0.167	0.186	0.236	0.192	0.231	0.14	0.164
Accuracy	0.7	0.664	0.63	0.589	0.817	0.798	0.594	0.621	0.652	0.641	0.708	0.71
Error	0.3	0.336	0.37	0.411	0.183	0.202	0.406	0.379	0.348	0.36	0.292	0.291
Delong's test P value	Reference	Reference	0.364	0.12	<0.001	<0.001	0.09	0.032	<0.001	0.005	<0.001	<0.001
Integrated discrimination improvement (P value)	Reference	Reference	-0.174 (<0.001)	-0.117 (<0.001)	-0.133 (<0.001)	-0.099 (<0.001)	-0.185 (<0.001)	-0.129 (<0.001)	-0.196 (<0.001)	-0.159 (<0.001)	-0.04 (<0.001)	-0.037 (<0.001)

Five machine learning algorithms were used to train the prediction model: gradient boosting machine, random forest, extreme gradient boosting, neural networks with a single hidden layer, and naïve Bayes. For each algorithm, hyperparameters were optimised with 10 repeats of 10-fold cross-validation to maximise the area under the receiver operating characteristic curve (AUC) of the training model. The SMOTE subsampling method was utilised during training.

The performance of each prediction model was evaluated using the AUC in the internal/external testing/validation datasets. The optimal cut-off value for hip fracture risk classification was determined based on receiver operating characteristic analysis of the training dataset using Youden's index. The sensitivity, specificity, positive predictive value, negative predictive value, F1 statistic, accuracy, and error rate were evaluated. DeLong's test was used to compare AUCs. The net reclassification index was computed to assess whether predictions from one model significantly differed from those of another model.

Results

In total, the derivation cohort included 239 996 individuals. In the female cohort, 7.3% and 10.4% of individuals experienced hip fracture within 10- and 15-year follow-up periods, respectively. Fewer hip fracture cases were observed in the male cohort (3.7% and 5.4%, respectively). After exclusion of individuals lost to follow-up, the derivation cohort comprised 91 926 and 75 823 women and 69 125 and 52 345 men for 10- and 15-year prediction models, respectively (Tables 1a and 1b). Individuals in the external validation cohort were younger, had fewer hospitalisations prior to the index date, and had fewer hip fracture cases. Diagnosis and drug prescription records for some known risk factors of

TABLE 2b. Performance of hip fracture risk prediction models for women excluding those lost to follow-up

Performance	Stepwise selection by logistic regression		Gradient boosting machine		Random forest		Extreme gradient boosting		Neural networks with a single hidden layer		Naïve Bayes	
	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk
Training cohort												
Area under the curve (95% confidence interval)	0.823 (0.818-0.827)	0.823 (0.819-0.828)	0.806 (0.801-0.811)	0.81 (0.805-0.814)	0.997 (0.997-0.998)	0.997 (0.996-0.997)	0.798 (0.792-0.803)	0.807 (0.802-0.811)	0.806 (0.801-0.811)	0.816 (0.811-0.82)	0.534 (0.529-0.54)	0.66 (0.654-0.667)
Testing cohort												
Area under the curve (95% confidence interval)	0.815 (0.805-0.825)	0.815 (0.806-0.824)	0.798 (0.788-0.809)	0.806 (0.797-0.815)	0.769 (0.758-0.78)	0.779 (0.769-0.789)	0.787 (0.776-0.7796)	0.804 (0.794-0.813)	0.784 (0.774-0.795)	0.806 (0.797-0.816)	0.634 (0.619-0.649)	0.658 (0.645-0.671)
Sensitivity	0.727	0.73	0.749	0.717	0.34	0.545	0.734	0.695	0.728	0.733	0.763	0.605
Specificity	0.748	0.74	0.707	0.742	0.923	0.847	0.717	0.761	0.709	0.739	0.312	0.71
Positive predictive value	0.248	0.376	0.227	0.374	0.337	0.434	0.229	0.384	0.223	0.377	0.113	0.31
Negative predictive value	0.96	0.927	0.961	0.924	0.924	0.896	0.959	0.921	0.958	0.928	0.92	0.893
F1	0.37	0.497	0.348	0.492	0.338	0.483	0.349	0.495	0.341	0.498	0.197	0.41
Accuracy	0.745	0.738	0.712	0.738	0.863	0.793	0.719	0.749	0.711	0.738	0.358	0.692
Error	0.255	0.262	0.288	0.262	0.137	0.207	0.281	0.251	0.289	0.262	0.642	0.308
External validation cohort												
Area under the curve (95% confidence interval)	0.841 (0.807-0.876)	0.845 (0.815-0.874)	0.845 (0.811-0.879)	0.843 (0.813-0.873)	0.773 (0.736-0.81)	0.783 (0.748-0.819)	0.837 (0.802-0.873)	0.84 (0.809-0.871)	0.806 (0.768-0.844)	0.838 (0.806-0.869)	0.595 (0.537-0.654)	0.64 (0.594-0.686)
Sensitivity	0.69	0.716	0.773	0.72	0.366	0.569	0.765	0.697	0.738	0.716	0.724	0.573
Specificity	0.814	0.818	0.762	0.813	0.908	0.838	0.77	0.823	0.777	0.803	0.238	0.745
Positive predictive value	0.221	0.349	0.199	0.344	0.233	0.324	0.203	0.348	0.202	0.331	0.068	0.234
Negative predictive value	0.972	0.955	0.978	0.955	0.949	0.935	0.977	0.952	0.975	0.954	0.918	0.928
F1	0.335	0.469	0.317	0.466	0.285	0.412	0.321	0.464	0.318	0.453	0.124	0.332
Accuracy	0.805	0.806	0.763	0.802	0.87	0.806	0.769	0.808	0.774	0.793	0.272	0.724
Error	0.195	0.194	0.237	0.198	0.13	0.194	0.231	0.192	0.226	0.207	0.728	0.276
Delong's test P value	Reference	Reference	0.469	0.618	<0.001	<0.001	0.556	0.351	<0.001	0.18	<0.001	<0.001
Integrated discrimination improvement (P value)	Reference	Reference	-0.428 (<0.001)	-0.517 (0.001)	-0.364 (<0.001)	-0.501 (0.001)	-0.445 (<0.001)	-0.533 (<0.001)	-0.455 (<0.001)	-0.567 (<0.001)	-0.089 (0.005)	-0.225 (<0.001)

fracture were less prevalent.

In the female prediction model, 239 potential predictors were used. The LR approach had the highest AUC in the external validation cohort for the 10-year (0.769) and 15-year (0.724) prediction models (Table 2a). After exclusion of individuals lost to follow-up, 233 potential predictors were used. The gradient boosting machine model had the highest AUC in external validation (0.841) for predicting 10-year risk, but DeLong's test showed no significant difference relative to LR (Table 2b). Both the LR approach and gradient boosting machine model achieved moderate sensitivity and specificity (>0.70). For predicting 15-year risk, the LR approach provided the best AUC (0.845) in the external validation cohort, attaining high specificity (0.818) and moderate sensitivity (0.716).

DeLong's test showed that the LR approach had a significantly higher AUC compared with the random forest, neural networks, and naïve Bayes models. Using the LR approach as reference, all other prediction models displayed significant and negative integrated discrimination improvement, indicating that the LR approach had better discrimination performance in predicting hip fracture risk. The LR approach identified 20 risk factors for women: age, number of hospitalisations, and diagnosis/drug prescription variables for accidental falls, heart disease, diabetes, Parkinson's disease, chronic kidney disease, psychoses, chronic obstructive pulmonary disease, depression, epilepsy, nutritional deficiencies, and history of fracture.

In the male prediction model, 238 potential predictors were used. For predicting 10-year risk, the LR approach had the highest AUC (0.805) in the external validation cohort; its sensitivity and specificity were moderate (>0.7). The LR approach also yielded the best AUC (0.723) in external validation for predicting the 15-year risk, although its sensitivity was lower than that of the 10-year

TABLE 3a. Performance of hip fracture risk prediction models for men.

Performance	Stepwise selection by logistic regression		Gradient boosting machine		Random forest		Extreme gradient boosting		Neural networks with a single hidden layer		Naïve Bayes	
	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk
Training cohort												
Area under the curve (95% confidence interval)	0.726 (0.717-0.734)	0.668 (0.661-0.676)	0.665 (0.656-0.675)	0.614 (0.605-0.622)	0.996 (0.995-0.997)	0.995 (0.994-0.995)	0.645 (0.635-0.655)	0.595 (0.587-0.603)	0.689 (0.68-0.697)	0.652 (0.644-0.66)	0.507 (0.497-0.518)	0.504 (0.495-0.513)
Testing cohort												
Area under the curve (95% confidence interval)	0.703 (0.687-0.72)	0.673 (0.658-0.688)	0.664 (0.645-0.683)	0.628 (0.612-0.644)	0.625 (0.608-0.643)	0.575 (0.56-0.591)	0.644 (0.625-0.644)	0.607 (0.591-0.624)	0.678 (0.661-0.695)	0.651 (0.635-0.667)	0.50 (0.5-0.5)	0.497 (0.48-0.514)
Sensitivity	0.705	0.642	0.658	0.733	0.05	0.097	0.556	0.627	0.81	0. 662	0.642	0.627
Specificity	0.614	0.613	0.611	0.482	0.963	0.919	0.68	0.55	0.476	0.578	0.352	0.363
Positive predictive value	0.066	0.0874	0.062	0.075	0.049	0.064	0.063	0.07314	0.057	0.082	0.037	0.053
Negative predictive value	0.982	0.968	0.979	0.969	0.963	0.947	0.975	0.963	0.985	0.968	0.962	0.945
F1	0.121	0.153	0.113	0.136	0.049	0.077	0.114	0.132	0.106	0.147	0.07	0.098
Accuracy	0.617	0.614	0.613	0.496	0.929	0.875	0.676	0.554	0.488	0.583	0.363	0.377
Error	0.383	0.386	0.387	0.504	0.071	0.125	0.324	0.446	0.512	0.418	0.637	0.622
External validation cohort												
Area under the curve (95% confidence interval)	0.805 (0.734-0.876)	0.723 (0.655-0.791)	0.71 (0.602-0.818)	0.684 (0.607-0.761)	0.655 (0.594-0.717)	0.62 (0.548-0.692)	0.692 (0.583-0.802)	0.672 (0.59-0.754)	0.701 (0.62-0.783)	0.707 (0.633-0.78)	0.5 (0.5-0.5)	0.55 (0.461-0.639)
Sensitivity	0.75	0.69	0.722	0.741	0.167	0.362	0.694	0.741	0.806	0.672	0.667	0.724
Specificity	0.718	0.716	0.6547	0.494	0.895	0.783	0.712	0.514	0.514	0.606	0.239	0.25
Positive predictive value	0.072	0.104	0.057	0.065	0.044	0.074	0.065	0.0676	0.046	0.075	0.025	0.044
Negative predictive value	0.99	0.98	0.988	0.976	0.974	0.963	0.988	0.977	0.989	0.975	0.961	0.95
F1	0.131	0.18	0.106	0.12	0.07	0.122	0.12	0.124	0.087	0.135	0.048	0.083
Accuracy	0.719	0.715	0.656	0.505	0.875	0.764	0.712	0.524	0.522	0.609	0.251	0.272
Error	0.281	0.285	0.344	0.495	0.125	0.236	0.288	0.476	0.478	0.391	0.749	0.728
Delong's test P value	Reference	Reference	0.04	0.275	<0.001	0.023	0.024	0.209	0.013	0.523	<0.001	0.002
Integrated discrimination improvement (P value)	Reference	Reference	-0.135 (<0.001)	-0.083 (<0.001)	-0.082 (<0.001)	-0.109 (<0.001)	-0.136 (<0.001)	-0.088 (<0.001)	-0.171 (<0.001)	-0.138 (<0.001)	-0.036 (<0.001)	-0.022 (<0.001)

prediction model (Table 3a). After exclusion of individuals lost to follow-up, 233 potential predictors were included in model development. The LR approach displayed the best AUCs in external validation: 0.898 for 10 years and 0.843 for 15 years. Both sensitivity and specificity were >0.8 in predicting the 10-year risk, but the sensitivity for the 15-year prediction model dropped below 0.7 (Table 3b).

DeLong's test showed that the LR approach had a significantly higher AUC compared with the random forest and naïve Bayes models. The LR approach had better discrimination performance in predicting hip fracture risk; all other prediction models showed significant and negative integrated discrimination improvement with reference to the LR approach. The LR approach identified 20 risk factors for men: age, number of hospitalisations, and diagnosis/drug prescription variables for heart disease, diabetes, Parkinson's disease, chronic kidney disease, psychoses, chronic obstructive pulmonary disease, depression, epilepsy, nutritional deficiencies, and history of fracture.

Discussion

In a German osteoporotic hip fracture prediction model involving 288 086 individuals, age, sex, history of fracture, and medication were identified as predictors. The model had an AUC of 0.65 to 0.7.[5] The use of a pre-defined set of risk factors to train the prediction model may exclude strong risk factors not collected in past studies. Therefore, our study included all diagnosis and drug prescription records as potential predictors. After exclusion of individuals lost to follow-up, our best-performing prediction models attained AUCs >0.8 in external validation, indicating clinical utility. Notably, the external validation cohort comprised community-dwelling individuals, demonstrating the high generalisability

TABLE 3b. Performance of hip fracture risk prediction models for men excluding those lost to follow-up

Performance	Stepwise selection by logistic regression		Gradient boosting machine		Random forest		Extreme gradient boosting		Neural networks with a single hidden layer		Naïve Bayes	
	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk	10-year risk	15-year risk
Training cohort												
Area under the curve (95% confidence interval)	0.826 (0.819-0.834)	0.819 (0.812-0.825)	0.796 (0.788-0.804)	0.796 (0.79-0.803)	0.997 (0.996-0.998)	0.996 (0.995-0.997)	0.785 (0.777-0.794)	0.789 (0.782-0.796)	0.818 (0.81-0.825)	0.811 (0.804-0.817)	0.519 (0.512-0.526)	0.647 (0.638-0.657)
Testing cohort												
Area under the curve (95% confidence interval)	0.817 (0.801-0.834)	0.815 (0.801-0.829)	0.796 (0.779-0.813)	0.797 (0.783-0.812)	0.763 (0.746-0.78)	0.767 (0.752-0.781)	0.785 (0.767-0.802)	0.794 (0.779-0.808)	0.798 (0.782-0.815)	0.797 (0.783-0.812)	0.637 (0.613-0.66)	0.65 (0.631-0.669)
Sensitivity	0.743	0.748	0.719	0.708	0.321	0.484	0.707	0.692	0.73	0.722	0.801	0.564
Specificity	0.75	0.741	0.739	0.763	0.937	0.886	0.75	0.778	0.737	0.752	0.232	0.755
Positive predictive value	0.159	0.272	0.149	0.278	0.244	0.353	0.152	0.287	0.15	0.274	0.062	0.229
Negative predictive value	0.979	0.958	0.976	0.953	0.956	0.93	0.976	0.951	0.977	0.954	0.948	0.931
F1	0.262	0.399	0.246	0.399	0.277	0.408	0.251	0.406	0.249	0.397	0.115	0.326
Accuracy	0.75	0.742	0.738	0.757	0.9	0.84	0.748	0.768	0.737	0.749	0.266	0.733
Error	0.25	0.258	0.262	0.243	0.1	0.16	0.252	0.232	0.263	0.251	0.734	0.267
External validation cohort												
Area under the curve (95% confidence interval)	0.898 (0.857-0.939)	0.843 (0.788-0.898)	0.854 (0.787-0.921)	0.84 (0.7854-0.896)	0.758 (0.692-0.825)	0.775 (0.711-0.84)	0.809 (0.72-0.897)	0.818 (0.759-0.878)	0.865 (0.796-0.935)	0.832 (0.77-0.893)	0.573 (0.444-0.702)	0.678 (0.596-0.759)
Sensitivity	0.806	0.707	0.722	0.707	0.306	0.483	0.778	0.672	0.778	0.707	0.667	0.534
Specificity	0.816	0.802	0.771	0.786	0.882	0.865	0.776	0.8	0.798	0.781	0.199	0.816
Positive predictive value	0.139	0.21	0.104	0.198	0.087	0.211	0.114	0.201	0.125	0.194	0.03	0.178
Negative predictive value	0.991	0.973	0.987	0.973	0.972	0.957	0.99	0.97	0.99	0.973	0.941	0.959
F1	0.238	0.324	0.182	0.309	0.136	0.293	0.199	0.31	0.215	0.305	0.057	0.267
Accuracy	0.816	0.795	0.769	0.781	0.861	0.838	0.776	0.791	0.798	0.776	0.215	0.796
Error	0.184	0.205	0.231	0.219	0.139	0.162	0.224	0.209	0.202	0.224	0.785	0.204
Delong's test P value	Reference	Reference	0.102	0.806	<0.001	0.027	0.023	0.15	0.211	0.5	<0.001	<0.001
Integrated discrimination improvement (P value)	Reference	Reference	-0.427 (<0.001)	-0.435 (<0.001)	-0.339 (<0.001)	-0.426 (<0.001)	-0.434 (<0.001)	-0.445 (<0.001)	-0.526 (<0.001)	-0.502 (<0.001)	-0.117 (0.025)	-0.271 (<0.001)

of our prediction models. Additionally, the prediction model did not use BMD as a predictor, owing to the limited availability of dual-energy X-ray absorptiometry in Hong Kong.

Using a data-driven approach that does not rely on known associations between predictor variables and fracture, some novel predictors were identified. One example was the diagnosis or drug prescription for anaemias and other blood disorders, which were associated with higher odds of hip fracture. This finding is consistent with the results of our Mendelian randomisation study, which demonstrated a positive causal association of genetically determined red blood cell traits with BMD. Individuals with haematological diseases (eg, anaemia) may have higher lifelong risks of osteoporosis and fracture. Other novel predictors, such as the use of emollient and barrier preparations, laxatives, and vitamins/minerals, were indicators of ageing or frailty; they were usually prescribed for dry skin, constipation, and poor appetite. The underlying mechanisms of how these novel predictors affect fracture risk warrant future investigation.

Model performance may be further improved by including medical records from >1 year prior to the index date, and by incorporating medical information such as laboratory test results and surgical procedures. With additional validation in independent cohorts from the Hong Kong population, these prediction models may serve as routine screening tools in future public healthcare settings.

Conclusions

We developed ethnicity- and sex-specific hip fracture prediction models for the Hong Kong population using machine learning algorithms and electronic medical records. The prediction models demonstrated good performance, achieving AUCs

>0.8. The prediction models may be clinically useful and generalisable to the public.

Funding

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Disclosure

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1. Li GH, Cheung CL, Tan KC, et al. Development and validation of sex-specific hip fracture prediction models using electronic health records: a retrospective, population-based cohort study. EClinicalMedicine 2023;58:101876.

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Survival estimate models of cancer patients with spinal metastases: big data analytics to aid daily clinical practice (abridged secondary publication)

KYH Kwan *, CL Cheung, KMC Cheung, R Luo, DMC Poon, TW Lam, TC Lam

KEY MESSAGE

We used machine learning to predict 6-month survival after radiotherapy in 10 537 patients with spinal metastases. Our model demonstrated 88.5% accuracy in distinguishing survival outcomes. Its promising performance could enhance decision making for radiotherapy.

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Introduction

Spinal metastases affect 60% to 70% of patients with advanced cancer.[1] Malignant spinal cord compression is associated with high morbidity and mortality.[2] To mitigate the adverse outcomes of spinal metastases, intensification of radiotherapy and surgery is proposed in addition to chemotherapy. Radiotherapy is utilised to control pain and improve outcomes in spinal metastasis.[3] Decision making regarding surgery for spinal metastases is complex. Treatment intensification is associated with substantial morbidity and mortality, particularly for spinal surgery.[4,5] Surgeries in an emergency setting are resource-intensive, requiring specialised surgeons and prolonged postoperative rehabilitation.[6] Similarly, intensification of radiotherapy using stereotactic body radiotherapy enables excellent local tumour control.[7] However, it requires increased resources in imaging and dosimetry, which are scarce in public hospital settings. Therefore, an accurate survival estimate is essential for the spinal care team to determine the most appropriate treatment for this heterogeneous patient group. For patients with short survival of ≤3 months,[8] invasive treatment with major decompressive surgery near the end of life is likely to cause major morbidity and prolonged hospitalisation. Conventional palliative radiotherapy alone, delivered in 10 fractions, is sufficient for pain relief and stabilisation in 70% of patients.[9] For patients with longer estimated survival, treatment intensification is deemed necessary to mitigate severe complications of spinal metastases, which can lead to irreversible lower limb paralysis.[10]

This study aimed to construct an accurate survival prediction model based on a cohort of approximately 10 000 patients with spinal metastases in Hong Kong, who exhibit heterogeneous backgrounds and outcomes.

TABLE 1. Model performance across various evaluation metrics.

Metrics	438 features	Top 50 features	Top 40 features	Top 30 features	Top 20 features	Top 15 features	Top10 features
Area under the receiver operating characteristic curve	0.885	0.879	0.879	0.879	0.871	0.864	0.839
Log-loss	0.421	0.433	0.438	0.436	0.447	0.464	0.495
Root mean square error	0.1353	0.140	0.141	0.141	0.144	0.148	0.162
Precision-recall	0.804	0.801	0.796	0.796	0.795	0.790	0.761
F1 Score	0.825	0.822	0.818	0.818	0.817	0.813	0.788

Methods

We constructed a prediction model using the Light Gradient Boosting Machine (a Microsoft-developed gradient boosting framework) for structured data and the bag-of-words model for unstructured data. The Light Gradient Boosting Machine is recognised for its advanced network communication, efficient memory utilisation, rapid training process, and effective overfitting prevention measures, facilitated by a histogram-based algorithm, leaf-wise growth strategy, gradient-based one-side sampling, and exclusive feature bundling. These mechanisms provide efficient solutions for high-dimensional datasets. For text data, we used the bag-of-words model to transform raw text into term frequency matrices, using a 10-fold cross-validation approach for model evaluation. Model optimisation was achieved through hyperparameter tuning using grid search and refinement of feature extraction from unstructured text. This process involved creating a 'stop words' list and incorporating n-grams of varying lengths to capture more meaningful information. The model was designed to maximise prediction accuracy while maintaining robustness and generalisability.

Results

After matching each patient with a unique reference key and excluding those with missing data, we obtained 10 537 unique reference keys. Each patient was treated as a unit of observation in the prediction problem: patient data collected prior to the diagnosis date were used to construct the independent variables, whereas

TABLE 2. The 10 most relevant features for survival after radiotherapy in our model.

Feature	Split	Gain	Quantile	Types	Explanation
Albumin	284.2	9.87	11.0-55.0 g/L	Numerical	Total amount of albumin in the blood (last test result before radiotherapy or most recent result)
lnratio_ab	237.6	7.63	0-12	Numerical	Neutrophil-to-lymphocyte ratio (absolute lymphocyte and absolute neutrophil counts from the last test result before radiotherapy or most recent result)
Codes_v66_7	168.4	7.43	0-35 times	Numerical	Number of inpatient diagnosis/prognosis codes (ICD-9-CM Diagnosis Code V66.7: encounter for palliative care)
Sodium	233.6	3.79	108.12-159 mmol/L	Numerical	Amount of sodium in the blood (last test result before radiotherapy or most recent result)
Codes_486	124.4	3.21	0-16 times	Numerical	Number of inpatient diagnosis/prognosis codes (ICD-9-CM Diagnosis Code 48.6: other resection of the rectum)
Duration_between_ip_and_RT	205	2.93	0-688 days	Numerical	Number of days between the discharge date of the latest hospitalisation before radiotherapy and the radiotherapy date
Codes_99_25	202.8	2.10	0-72 times	Numerical	Number of inpatient diagnosis/prognosis codes (ICD-9-CM Diagnosis Code 99.25: injection or infusion of a cancer chemotherapeutic substance)
Alkaline phosphatase	291	2.09	17-5971 U/L	Numerical	Amount of alkaline phosphatase in the blood. This enzyme is predominantly found in the liver, bones, kidneys, and digestive system. When the liver is damaged, alkaline phosphatase may leak into the bloodstream (last test result before radiotherapy or most recent result).
Codes_198_5	179.2	2.04	0-99 times	Numerical	Number of inpatient diagnosis/prognosis codes (ICD-9-CM Diagnosis Code 198.5: secondary malignant neoplasm of bone and bone marrow)
Phosphate	314	2.03	0.19-3.94 U/L	Numerical	A phosphate test measures the amount of phosphate in your blood (the last test result before radiotherapy or the latest one).

survival status 6 months after assessment served as the dependent variable.

The mean age of the 10 537 patients with spinal metastases was 64±13 (range, 5-101) years. Using one-hot encoding, independent variables were split into 3248 features. The importance of these features was ranked based on the amount of information gained. The model was then trained using the 438 features for which information gain was >0. The area under the receiver operating characteristic curve was the primary metric for assessing model performance in classification. The overall score of the model was 0.885. Other metrics including log-loss, root mean square error, precision-recall, and F1 score served as auxiliary measurement metrics. The performance metrics for this model, as well as those for models using only the top 50, 40, 30, 20, 15, and 10 features, respectively, are shown in Table 1. The most important feature was the total amount of albumin in the blood from the last test result before radiotherapy (or the most recent result). Discussions with practitioners confirmed that the top 10 features were most relevant for survival after radiotherapy (Table 2).

Conclusion

We used machine learning to predict 6-month survival rates after radiotherapy in patients with spinal metastases, based on a dataset of 10 537 patients. Our model demonstrated 88.5% accuracy in distinguishing survival outcomes. Its promising performance could enhance decision making for radiotherapy.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#07181576). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

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Genetic diagnosis for osteogenesis imperfecta: abridged secondary publication

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KEY MESSAGES

1. Osteogenesis imperfecta (OI) is a rare hereditary connective tissue disorder, with an incidence of one in 15 000 to 20 000 newborns.
2. Identification of pathogenic mutations and genotype-phenotype correlations in Chinese patients with OI would expand the mutational spectrum of causative genes and enhance our understanding of bone development, enabling optimisation of targeted molecular-based therapies.
3. In patients with OI in southern China, variants in *COL1A1*, *COL1A2*, *IFITM5*, *FKBP10*, *WNT1*, and *P4HB* were identified. Correlations between genotype and clinical manifestations were also investigated to improve medical care.

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Introduction

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a rare hereditary bone dysplasia typically manifesting as skeletal fragility, deformity, and growth deficiency, with an incidence of 1 in 15 000 to 20 000 newborns. The clinical features of this connective tissue disorder affect multiple organs including pulmonary dysfunction, cardiac defects, dentinogenesis imperfecta, joint hypermobility, blue sclerae, and hearing loss.[1,2] OI is an autosomal dominant disease caused by *COL1A1* and *COL1A2*; other dominant and recessive genes related to diverse aspects of bone metabolism can also be involved, such as *CRTAP*, the first recessive gene known to cause lethal OI.[3] Newly identified recessive genes are designated with additional numbers for a more adaptive and comprehensive classification system. Current clinical therapies for OI are symptom-based and dependent on clinical severity. However, unclear effects on fracture occurrence and a lack of systemic clinical guidance for OI hinder their efficacy.[4] Identification of pathogenic mutations and genotype-phenotype correlations in Chinese patients would expand the mutational spectrum of causative genes and enhance our understanding of bone development, enabling the optimisation of targeted molecular-based therapies. This study aimed to identify causative mutations in an OI cohort to promote patient-centred medical care.

Methods

We recruited >200 patients with OI (including 80 patients and their parents/siblings) at The University of Hong Kong–Shenzhen Hospital for genetic diagnosis. We performed targeted amplicon sequencing to identify variants in genes present in most patients. Variants were identified based on specific variant filtration criteria. Detailed clinical features were documented by a panel of clinicians. We examined risk variant pathogenicity using a variety of cellular assays, including minigene splicing, luciferase, and scrambled RNase A assays. After the necessary procedures, human samples were collected for histological analyses.

Results

An OI genetic diagnosis workflow was used for variant identification (Fig). Considering the cost-effectiveness of genetic testing for most families, we first performed targeted amplicon sequencing to identify variants in genes present in most patients. We found that 119 patients carried pathogenic mutations in *COL1A1* (n=61), *COL1A2* (n=56), or both (n=2). These OI-COL1 patients predominantly demonstrated clinical subtypes I and IV. Six patients harbouring biallelic variants in *FKBP10* were identified: three children from a consanguineous family had a homozygous variant of *FKBP10* (c.918-3C>G) and another three patients diagnosed with OI had biallelic variants of *FKBP10*. Additionally, 23 patients were confirmed to have the *IFITM5* c.-14C>T mutation. Type V patients accounted for 10.6% of our cohort, comparable to the reported prevalence of type V OI among individuals of Chinese ethnicity. Of 25 (10.3%) patients harbouring pathogenic variants in the *WNT1* locus, 19 displayed

compound heterozygous variants and six showed homozygous variants. Moreover, two *de novo* heterozygous *P4HB* missense variants (c.524C>A, p.Ala175Glu and c.1200C>G, p.Cys400Trp) were identified in two unrelated patients with moderate OI.

Twenty critical clinical traits for OI patients, including blue sclerae, dentinogenesis imperfecta, hearing loss, and joint and skeletal abnormalities, were recorded. Bones from affected individuals displayed increasing porosity with disorganised collagen alignment from type I to types III and IV, suggesting that the severity of clinical manifestations was positively correlated with the degree of abnormal bone geometry. Missense mutations in *COL1A1/2* were associated with more severe clinical phenotypes.

The homozygous variant of *FKBP10* (c.918-3C>G) caused retention of intron 5 and deletion of exon 6 in the *FKBP10* mRNA isoforms. Compared with control cells, no FKBP65 protein could be detected in the mutant osteoblasts. These findings suggest that abnormal mRNA splicing results in a truncated FKBP65 protein. Compared with bone histology from a normal sample, the increased porosity in the cortical bones of *FKBP10* patients resulted in abnormal bone geometry, reduced mechanical toughness, and skeletal deformity.

WNT1 proteins could be detected after transfection with wild-type and mutant vectors. Four intact shifting bands indicated post-translational N-glycosylation required for WNT1 secretion.[5] Other than p.C151Y and p.S295L, most variants substantially affected WNT1 secretion capacity. WNT1 functions as an important ligand to activate the WNT/β-catenin signalling pathway. We measured WNT signalling activity induction by various mutant forms of WNT1. The transactivation function of this ligand was severely compromised by different amino acid substitutions. We measured the transcription level of *Axin2* to examine the cellular impact of WNT1 variants. Variants including p.G169D and p.L257P retained partial WNT1 transactivation activity. Other variants considerably reduced the mRNA level of *Axin2*.

To characterise *P4HB* variants, we first overexpressed PDI-Myc fusion protein in MC3T3 cells to observe the mutational impact on protein expression. An obvious additional band with high molecular weight (>170 kDa) appeared in PDI-Glu175 under both reducing and non-reducing conditions. Such strong intermolecular forces could only be disrupted after prolonging the boiling time during protein sample preparation. We next performed a co-immunoprecipitation assay to clarify the nature of the macromolecular complex. Consistent molecular weight band patterns suggested that the relevant component of the macromolecular

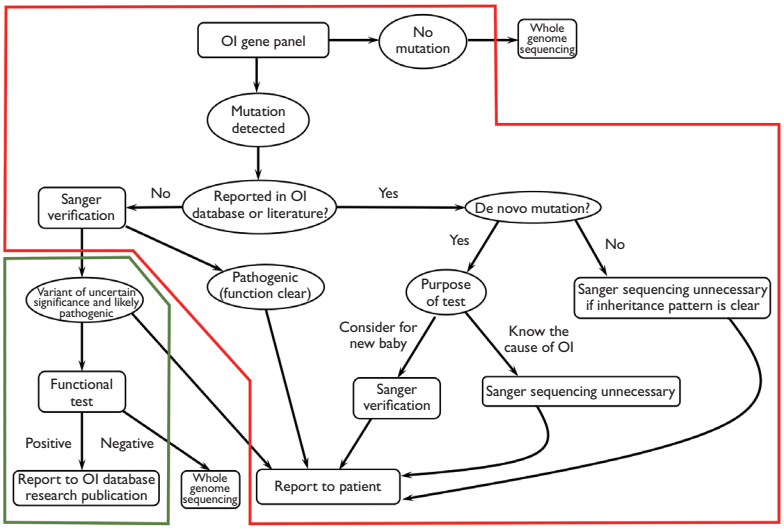

FIG. Flowchart depicting genetic diagnosis for patients with osteogenesis imperfecta (OI).

complex is a tetramer. The catalytic and chaperone functions of PDI homopolymers are substantially diminished due to the covering of substrate-binding sites. Isomerase activity was considered to indicate its biochemical function. We directly used proteins competitively eluted from A/G agarose beads (retaining the presence of tetramers) to reactivate scrambled RNase A. The results indicated that the isomerase activities of these two mutant forms were both reduced, but the function of PDI-Trp400 was more severely impaired.

Discussion

Considering the complex clinical and genetic features of OI, genotyping facilitates accurate diagnosis and informed genetic counselling. We detected a correlation between genotype and phenotype. We identified 102 unique mutations in *COL1A1* and *COL1A2*—most patients (63.6%, 119/187) carried variants in type I collagen. The relationship between genetic mutations and clinical severity in OI patients is complex, such that glycine substitutions and splicing mutations are the dominant variants, due to either structural defects (qualitative) or quantitative changes in type I collagen. Mild OI cases were caused by both quantitative and qualitative defects in type I collagen. Bisphosphonate treatment improved bone mineral density, particularly in patients aged 10 to 15 years; however, the effects of treatment on height were minimal.

We found that type V OI caused by the *IFITM5* (c.-14C>T) mutation was present in 10.6% of patients. Six patients with autosomal recessive variants

of *FKBP10* were identified; two of the variants (c.745C>T and c.825dupC) have not been previously reported. The c.918-3C>G variant resulted in intron retention and exon skipping during *FKBP10* mRNA splicing.

Our genetic analysis also identified 25 patients harbouring *WNT1* variants and two patients harbouring *P4HB* variants. Patients with *WNT1* variants primarily displayed moderate (type IV) to severe (type III) symptoms, whereas those with *COL1A1* and *COL1A2* variants predominantly exhibited types I and IV symptoms. This supports the association of autosomal recessive OI with more severe phenotypes. Secreted WNT ligands are cysteine-rich lipoproteins that bind to the Frizzled receptor and co-receptors (LRP5/6), triggering downstream pathways. Our mutagenesis assay indicated that amino acid substitutions in the WNT1 protein altered its secretory capacity and signalling activity, resulting in a wide spectrum of skeletal deformities. A more pronounced discrepancy was observed in the luciferase assay, implying that the variants have detrimental effects on WNT1 binding affinity and signalling activation.

P4HB encodes PDI, which can function as a monomeric oxidoreductase and molecular chaperone to catalyse the formation of inter-chain disulfide bonds for collagen fibril stabilisation and to prevent aggregation of premature triple helices, respectively. Moreover, PDI is identical to the beta subunit of prolyl 4-hydroxylase, a crucial enzyme responsible for proline residue hydroxylation during post-translational modification of collagen alpha chains. A stable complex was formed after substitution of the amino acid p.A175E. These two variants disrupted the biochemical functions of PDI. Dimers and even tetramers of PDI have repeatedly been reported, but the monomer is the most active form, suggesting that multimerisation weakens its substrate-binding capabilities. The variant p.C400W substitutes the second cysteine residue of the CGHC catalytic motif in PDI, leading to disruption of the disulfide bond between the two cysteine residues in the oxidised state. Thus, its deleterious effect on the function of PDI is more pronounced. Conceivably, therefore, *WNT1* and *P4HB* variants identified in our cohort might contribute to dysfunctions regarding bone formation and differentiation through multiple pathways.

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This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#07181676). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Chen P, Tan Z, Shek HT, et al. Phenotypic spectrum and molecular basis in a Chinese cohort of osteogenesis imperfecta with mutations in type I collagen. Front Genet 2022;13:816078.
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Multicomponent intervention for family caregivers of dementia: a randomised controlled trial using the multiphase optimisation strategy (abridged secondary publication)

KL Chou *, KSL Cheung, JYY Kwok, BHP Lau, S Zarit, VW Lou, ST Cheng, D Cheung, D Gallagher Thompson

KEY MESSAGES

1. The multiphase optimisation strategy, combined with fractional factorial design, was used to assess the effects of each intervention component on distressed primary family caregivers of individuals with dementia in Hong Kong.
2. Over 12 months, intervention components of mindfulness-based intervention, support group, behavioural activation, and behavioural problems management led to improvements in dementia management strategies, mindfulness attention awareness, psychological well-being, and functional social support, while reducing anxiety and depression symptoms.

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Introduction

Dementia places a considerable burden on family members who provide care for individuals affected by the condition.[1] Effective interventions are needed to alleviate the adverse effect of caregiving on family caregivers. This study aimed to identify the effective components of a multicomponent intervention for caregivers of individuals with dementia in Hong Kong using the multiphase optimisation strategy.[2]

Methods

This prospective, assessor-blinded, randomised controlled trial used the multiphase optimisation strategy to evaluate the effects of five intervention components: self-care skills, behavioural problems management, behavioural activation, mindfulness-based intervention, and support group. Chinese primary family caregivers for individuals with dementia were recruited in Hong Kong. They were aged ≥18 years, were spouse, adult child, or child-in-law of a care recipient, had no cognitive impairment (based on the Hong Kong version of Montreal Cognitive Assessment 5-Min), provided care for ≥20 hours per week for ≥1 year, involved in assisting with activities of daily living and instrumental activities of daily living, and experienced a certain level of depression or burden (indicated by Patient Health Questionnaire-9 score of >9 or Zarit Burden Interview score of >18) to ensure sample homogeneity.[3,4]

Participants were assessed at baseline and received education on dementia and caregiving. They were then randomly assigned using the fractional factorial design to one of the 16 experimental conditions that varied in the delivery of treatment components. Implementation fidelity of all five components was ensured, and adherence to the protocol was monitored. Assessments were conducted at baseline, 6 months, and 12 months. Primary outcome measures included the physical domain of the Short Form-12 Health Survey, the Zarit Burden Interview, the Perceived Stress Scale, Ryff's Psychological Well-Being Scale, the Chinese version of the Anxiety Subscale of the Hospital Anxiety and Depression Scale, the Chinese version of the Patient Health Questionnaire, and the Medical Outcomes Study Social Support Survey. Proximal outcome measures included the self-care subscale in the Risk Appraisal Measure, the criticism, encouragement, and active management domains of the Dementia Management Strategies Scale, the number of meaningful or joyful events over the past

2 weeks, the Five Facet Mindfulness Questionnaire, and satisfaction with the support group.

The intention-to-treat approach was used; all participants were included in the analysis regardless of intervention receipt or study withdrawal. A total of 14 regression models were analysed regarding changes in primary and proximal outcome scores from baseline to 12-month follow-up relative to the five intervention components. Moderation and mediation effects were also examined.

Results

In total, 171 female and 79 male caregivers (mean age, 48.9±13.8 years) of individuals with dementia (mean age, 76.7±8.9 years) participated in all intervention sessions and were assessed at 6 months (n=245) and 12 months (n=235). Nearly 90% of the caregivers were either adult children or children-in-law of the care recipients. They spent approximately 59.5 hours per week on caregiving. The implementation fidelity of all five components was equally high; participants were satisfied with the quality of the intervention.

Over 12 months, participants who received the mindfulness-based intervention component demonstrated a reduction in anxiety symptoms (β= -1.07, P=0.029) and depression symptoms (β= -2.13, P<0.001). They also demonstrated increases in psychological well-being (β=3.00, P=0.029), functional social support (β=4.76, P=0.007), mindfulness attention awareness (β=4.23, P<0.001), dementia management strategies of active management (β=3.70, P<0.001), and satisfaction with the support group (β=1.97, P<0.001) [Table]. Participants who received the support group component reported an increase in functional

TABLE. Adjusted regression analyses for changes in primary and proximal outcomes from baseline to 12-month follow-up in terms of the five intervention components.

Intervention component	Model 1 (self-care skills)		Model 2 (behavioural problems management)		Model 3 (behavioural problems management)		Model 4 (behavioural activation)		Model 5 (mindfulness-based intervention)		Model 6 (mindfulness-based intervention)		Model 7 (support group)	
	Primary outcome													
	Physical domain of Short Form-12		Zarit Burden Interview		Perceived Stress Scale		Ryff's Psychological Well-Being Scale		Anxiety Subscale of the Hospital Anxiety and Depression Scale		Patient Health Questionnaire		Medical Outcomes Study Social Support Survey	
	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value
Self-care skills	0.36	0.640	1.07	0.258	0.70	0.284	0.05	0.973	0.00	0.999	-0.23	0.519	-0.03	0.985
Behavioural problems management	0.58	0.439	-0.21	0.825	-0.05	0.935	3.52	0.008	0.56	0.233	-0.38	0.292	2.89	0.088
Behavioural activation	-1.51	0.048	-1.56	0.099	-1.32	0.044	1.49	0.265	-0.46	0.337	-0.29	0.426	1.22	0.475
Mindfulness-based intervention	1.17	0.135	1.42	0.145	0.66	0.326	3.00	0.029	-1.07	0.029	-2.13	<0.001	4.76	0.007
Support group	-0.06	0.938	1.18	0.200	-0.53	0.409	0.24	0.852	-0.06	0.896	0.35	0.327	4.63	0.006
	Model 8 (self-care skills)		Model 9 (behavioural problems management)		Model 10 (behavioural problems management)		Model 11 (behavioural problems management)		Model 12 (behavioural activation)		Model 13 (mindfulness-based intervention)		Model 14 (support group)	
	Proximal outcome													
	Self-care subscale in the Risk Appraisal Measure		Dementia Management Strategies Scale–Criticism		Dementia Management Strategies Scale–Encouragement		Dementia Management Strategies Scale–Active Management		No. of meaningful events		Five Facet Mindfulness Questionnaire		Satisfaction	
	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value
Self-care skills	0.57	0.119	0.54	0.582	0.26	0.770	-0.21	0.828	0.14	0.390	-0.49	0.629	-0.11	0.817
Behavioural problems management	-0.60	0.100	0.92	0.349	2.49	0.005	5.99	<0.001	0.29	0.072	1.98	0.048	-0.39	0.420
Behavioural activation	0.75	0.041	-0.96	0.331	0.34	0.708	-0.13	0.889	-0.31	0.056	-0.11	0.910	-0.17	0.732
Mindfulness-based intervention	-0.25	0.504	-0.29	0.779	1.75	0.058	3.70	<0.001	0.03	0.840	4.23	<0.001	1.97	<0.001
Support group	0.00	0.990	0.29	0.767	-1.17	0.181	-1.07	0.254	0.07	0.647	-1.01	0.303	-0.39	0.417

social support (β=4.63, P=0.006). Participants who received the behavioural activation component demonstrated a reduction in stress levels (β= -1.32, P=0.044). Participants who received the behavioural problems management component demonstrated an increase in psychological well-being (β=3.52, P=0.008), as well as improvements in dementia management strategies of encouragement (β=2.49, P=0.005) and active management (β=5.99, P<0.001) and in mindfulness attention awareness (β=1.98, P=0.048). Participants who received the self-care skills component did not result in significant improvement in primary or proximal outcome.

For mediational analysis, after controlling for changes in mindfulness attention awareness, the direct effect between the mindfulness-based intervention and changes in depression symptoms remained significant but decreased in magnitude (β= -1.81, P<0.001). These findings support a partial mediation model, indicating that the mindfulness attention awareness acts as a partial mediator.

For moderation analysis, there was no interaction effect among intervention components on primary and proximal outcomes. Similarly, baseline scores of physical health status, stress/burden, psychological well-being, anxiety/depressive symptoms, and social support did not significantly moderate the effects of the five intervention components on changes in scores from baseline to follow-up assessments.

Discussion

The mindfulness-based intervention component effectively contributed to a reduction in anxiety and depression symptoms, an increase in psychological well-being, and an increase in functional social support, as well as an increase in dementia management strategies of active management, mindfulness attention awareness, and satisfaction with the support group. The behavioural problems management component effectively contributed to an increase in psychological well-being as well as an increase in dementia management strategies of active management and mindfulness attention awareness. The support group component effectively contributed to an increase in functional social support. The behavioural activation component effectively contributed to a reduction in stress. The support group component effectively contributed to increased functional social support. Intervention programmes for distressed family caregivers of individuals with dementia should include components of mindfulness-based intervention and support group, which are cost-effective and can improve coping mechanisms and foster a supportive environment for their well-being. Inclusion of the components of behavioural problems management and behavioural activation can further enhance caregiver well-being and reduce stress. Future implementation of similar programmes should consider these success factors: organisational support with adequate resources, well-trained staff with ongoing supervision, implementation infrastructure, and comprehensive participant engagement strategies to ensure programme effectiveness and sustainability. Limitations of the present study included variability in intervention dosage, the absence of a comparison group, and limited measurement time points.

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1. Kwok JYY, Cheung DSK, Zarit S, et al. Multiphase optimization of a multicomponent intervention for informal dementia caregivers: a study protocol. Trials 2023;24:791.
2. Kwok JYY, Cheung DSK, Zarit S, et al. Multicomponent intervention for distressed informal caregivers of people with dementia: a randomized clinical trial. JAMA Netw Open 2025;8:e250069.

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Initiation of statin therapy in patients with diabetes mellitus: a target trial emulation study (abridged secondary publication)

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KEY MESSAGES

1. Initiation of statins in diabetic patients with baseline low-density lipoprotein cholesterol levels of 1.8 to 2.5 mmol/L was associated with reduced risks of incident cardiovascular diseases and all-cause mortality, without significant increases in the risks of myopathy or liver dysfunction.
2. Compared with initiation of statin therapy at a threshold of 2.6 mmol/L, initiation at a threshold of 1.8 mmol/L may provide additional benefits in preventing cardiovascular diseases and all-cause mortality among patients with diabetes.

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Introduction

The treatment of hyperlipidaemia can prevent cardiovascular diseases (CVDs) in patients with type 2 diabetes mellitus (T2DM). Statins are the most commonly used lipid-lowering agents for reduction of low-density lipoprotein cholesterol (LDL-C) levels. The optimal timing for statin initiation is important in clinical practice, depending on the balance among potential benefits, adverse events, and medical costs. The American College of Cardiology and the American Heart Association recommend initiating statins at LDL-C levels ≥1.8 mmol/L in patients aged 40 to 75 years with diabetes mellitus.[1] However, there are no definitive recommendations concerning the timing of statin initiation in non-Caucasian populations. In mainland China and Hong Kong, a less stringent treatment target of LDL-C <2.6 mmol/L is recommended for patients with T2DM; lipid-lowering treatment is initiated when the therapeutic target is not achieved. This study aimed to investigate the long-term effects of statin therapy in Chinese patients with T2DM using target trial emulation and population-based observational data.

Methods

Electronic medical records of patients aged ≥18 years with T2DM and LDL-C levels ≥1.8 mmol/L in each calendar month between January 2008 and December 2014 were included in the emulated randomised controlled trials. To enhance statistical power, a sequence of trials was conducted every calendar month to increase the number of initiators and cases.

Statin initiation was defined as any treatment with simvastatin, atorvastatin, fluvastatin, rosuvastatin, lovastatin, pitavastatin, pravastatin, or any combination at baseline. Patients were categorised into two groups according to baseline LDL-C levels (1.8-2.5 vs ≥2.6 mmol/L). Within each group, those who initiated statin therapy were compared with those who did not.

Outcome measures included the overall incidence of CVDs (including myocardial infarction, heart failure, and stroke), five subcategories of CVD (myocardial infarction, heart failure, stroke, ischaemic stroke, and haemorrhagic stroke), two major adverse events related to statin therapy (myopathies and liver dysfunction), and all-cause mortality. All patients were followed up until death, the occurrence of any outcome measure, or the end of the study, whichever happened first. To minimise potential confounding by undiagnosed disease at baseline, patients who experienced an outcome within the first year of follow-up were excluded from analysis.

The intention-to-treat effect and per-protocol effect of statin therapy were estimated and expressed as hazard ratios (HRs). Baseline covariates were selected based on a priori knowledge and included sex, age, smoking status, clinical parameters (systolic and diastolic blood pressure, haemoglobin A1c, triglyceride level, high-density lipoprotein

cholesterol, and estimated glomerular filtration rate), comorbidities (hypertension, peripheral vascular disease, atrial fibrillation, dyslipidaemia, asthma, chronic obstructive pulmonary disease, and dementia), drug history within the past year (aspirin, insulin, oral antidiabetic drugs, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics), and service utilisation.

The per-protocol analysis was conducted by artificially censoring participants who deviated from their assigned strategy unless a medical justification was present. For instance, among statin initiators at baseline, those who discontinued statins were censored unless cessation was related to the occurrence of myopathies or liver dysfunction. Among non-statin initiators at baseline, those who commenced statin therapy were censored unless there was an indication of dyslipidaemia. To adjust for selection bias introduced by the censoring process, each patient was weighted at each time point by the inverse probability of receiving their assigned treatment strategy, conditional on baseline and time-varying covariates.

Subgroup analyses were conducted at baseline according to sex, age, and 10-year CVD risk. Sensitivity analysis was conducted by extending the statin discontinuation gap from 1 month to 3 months. Additionally, to evaluate residual confounding by indication, sensitivity analysis was performed by excluding patients with high cholesterol levels (total cholesterol >6.2 mmol/L) at baseline.

Results

In the intention-to-treat analysis, over a mean follow-up duration of 6.7 years, the estimated HRs for CVD incidence associated with statin initiation were 0.78 (95% confidence interval [CI]=0.72-0.84) in patients with baseline LDL-C of 1.8-2.5 mmol/L and 0.90 (95% CI=0.88-0.92) in patients with baseline LDL-C of ≥2.6 mmol/L. In the per-protocol analysis, the respective HRs were 0.59 (95% CI=0.51-0.68) and 0.77 (95% CI=0.74-0.81) [Fig 1]. This risk reduction was consistently observed for CVD subtypes and all-cause mortality in both LDL-C groups; there was no significant increase in major adverse event risk (Fig 2). In the per-protocol analysis, the absolute 10-year risk difference for overall CVD was -7.1% (95% CI= -10.7% to -3.6%) in patients with baseline LDL-C of 1.8-2.5 mmol/L and -3.9% (95% CI= -5.1% to -2.7%) in patients with baseline LDL-C of ≥2.6 mmol/L. The benefits of statin use including reductions in overall CVD risk and all-cause mortality were also observed among patients aged ≥75 years at different LDL-C thresholds for statin initiation.

Discussion

Our findings align with current evidence that statins reduce CVD risk irrespective of baseline LDL-C; benefits were observed in all patients with pre-treatment LDL-C of ≥1.8 mmol/L. A meta-analysis found that the reduction in major adverse cardiovascular event risk per unit change in LDL-C was significant among patients who initiated LDL-C lowering at a threshold of 1.6 mmol/L; there was no increase in serious adverse event risk.[2] Early initiation of statins during disease progression may further reduce inflammation and improve endothelial function,[3] contributing to early prevention of CVDs.

Significant reductions in CVD and all-cause mortality risks were observed among patients aged ≥75 years who initiated statin treatment at different

	Intention-to-treat analysis		Per-protocol analysis	
	10-year risk difference (%)	Hazard ratio (95% confidence interval)	10-year risk difference (%)	Hazard ratio (95% confidence interval)
Baseline low-density lipoprotein cholesterol: 1.8-2.5 mmol/L				
Overall cardiovascular diseases	-3.5 (-4.7, -2.3)	0.78 (0.72, 0.84)	-7.1 (-10.7, -3.6)	0.59 (0.51, 0.68)
Myocardial infarction	-0.9 (-1.7, -0.2)	0.84 (0.74, 0.96)	-2.8 (-3.6, -2.0)	0.61 (0.39, 0.95)
Heart failure	-0.3 (-1.3, 0.7)	0.87 (0.77, 0.98)	-3.9 (-7.2, -0.6)	0.39 (0.23, 0.65)
Stroke	-3.1 (-3.8, -2.4)	0.72 (0.65, 0.80)	-8.1 (-9.7, -6.4)	0.41 (0.31, 0.55)
Ischaemic stroke	-1.5 (-2.1, -0.9)	0.65 (0.55, 0.76)	-2.9 (-4.3, -1.5)	0.41 (0.22, 0.76)
Haemorrhage	-0.5 (-0.7, -0.3)	0.73 (0.55, 0.98)	-1.6 (-1.9, -1.2)	0.24 (0.05, 1.12)
Myopathies	0.0 (-0.3, 0.3)	1.03 (0.74, 1.42)	0.3 (-0.8, 1.4)	0.45 (0.13, 1.50)
Liver dysfunction	-2.0 (-3.0, -1.1)	0.86 (0.79, 0.93)	-1.7 (-5.6, 2.1)	0.96 (0.71, 1.30)
Mortality	-2.5 (-3.7, -1.4)	0.80 (0.74, 0.86)	-4.3 (-8.5, -0.1)	0.70 (0.52, 0.94)
Baseline low-density lipoprotein cholesterol ≥2.6 mmol/L				
Overall cardiovascular diseases	-2.2 (-2.6, -1.8)	0.90 (0.88, 0.92)	-3.9 (-5.1, -2.7)	0.77 (0.74, 0.81)
Myocardial infarction	-1.0 (-1.2, -0.7)	0.86 (0.82, 0.89)	-1.9 (-2.6, -1.2)	0.68 (0.62, 0.75)
Heart failure	-0.8 (-1.1, -0.5)	0.91 (0.88, 0.95)	-2.4 (-3.1, -1.7)	0.69 (0.63, 0.75)
Stroke	-1.2 (-1.6, -0.9)	0.89 (0.87, 0.92)	-2.2 (-3.1, -1.3)	0.78 (0.73, 0.83)
Ischaemic stroke	-0.7 (-0.9, -0.5)	0.82 (0.78, 0.86)	-1.5 (-2.1, -0.9)	0.65 (0.58, 0.72)
Haemorrhage	-0.1 (-0.2, 0.0)	0.92 (0.85, 1.01)	-0.2 (-0.5, 0.1)	0.85 (0.69, 1.04)
Myopathies	0.0 (-0.2, 0.2)	1.02 (0.92, 1.13)	-0.2 (-0.4, 0.1)	0.87 (0.67, 1.14)
Liver dysfunction	-1.6 (-2.0, -1.3)	0.92 (0.89, 0.94)	-2.8 (-3.5, -2.2)	0.85 (0.80, 0.90)
Mortality	-1.5 (-1.9, -1.1)	0.92 (0.90, 0.94)	-3.4 (-4.1, -2.7)	0.81 (0.76, 0.86)

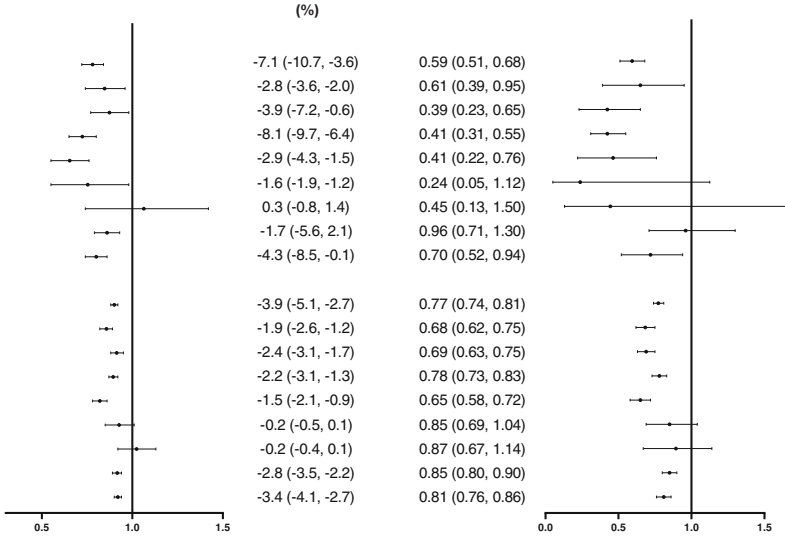

FIG 1. Hazard ratios and 10-year risk differences in the incidences of myocardial infarction, heart failure, stroke, major adverse events, and mortality between statin initiators and non-initiators.

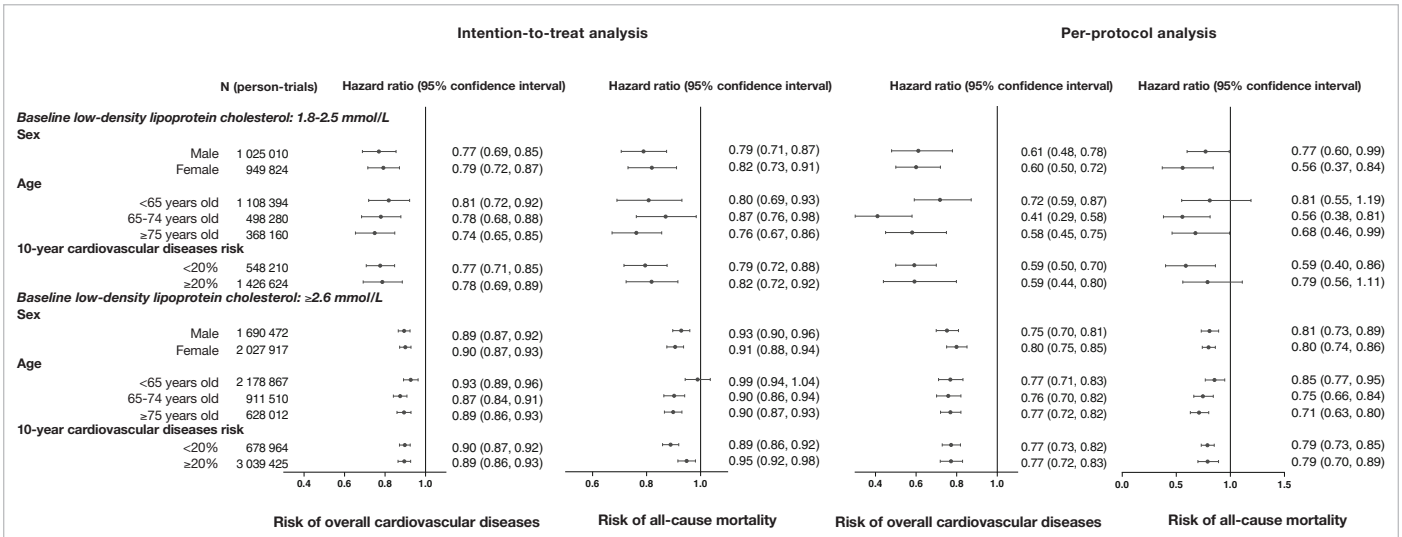

FIG 2. Hazard ratios for the effect of statin therapy on the incidences of myocardial infarction, heart failure, stroke, and mortality in subgroup analyses.

LDL-C levels. A meta-analysis showed that lipid-lowering treatment was similarly effective among patients aged >75 or <75 years in terms of reducing cardiovascular events (risk ratio=0.82, 95% CI=0.73-0.91).[4] Our findings indicate that statins are safe and effective for older adults aged ≥75 years with T2DM, although current guidelines provide no specific recommendations for this age group.

The anticipated adverse effects of statins may have limited their widespread use in real-world settings. However, statin use is not associated with increased risks of myopathy or liver dysfunction in Chinese patients.[5] Given the potential benefits of statins and the minimal adverse effects, statin therapy should be encouraged for CVD prevention in Chinese patients with T2DM.

Conclusion

Initiation of statin therapy in Chinese patients with T2DM and LDL-C levels of 1.8-2.5 mmol/L was associated with reduced risks of incident CVD and all-cause mortality, without significant increases in the risks of myopathy or liver dysfunction. Compared with initiation of statin therapy at an LDL-C level of 2.6 mmol/L, initiation at a threshold of 1.8 mmol/L may provide additional benefits in preventing CVDs and all-cause mortality.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#05190107). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Wan EYF, Xu W, Mok AHY, et al. Evaluating different low-density lipoprotein cholesterol thresholds to initiate statin for prevention of cardiovascular diseases in patients with type 2 diabetes mellitus: a target trial emulation study. Diabetes Obes Metab 2024;26:1877-87.

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Promoting advance care planning in people with early dementia and their family caregivers

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KEY MESSAGES

1. Advance care planning (ACP) allows people with early-stage dementia to plan for future care before they lose mental capacity.
2. A dyadic-based ACP programme facilitates discussions on future care between people with early-stage dementia and their family caregivers in a community care setting.
3. After the ACP programme, people with early-stage dementia reported significantly higher levels of self-efficacy and readiness for ACP. Concordance regarding end-of-life care preferences between participants and their family caregivers also significantly improved.
4. More services are needed to support the completion of advance directives in the community.

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Introduction

People with dementia experience increasing dependency due to declining physical and cognitive functions and decision-making abilities as the disease progresses. Consequently, the promotion of advance care planning (ACP) at an early stage of dementia is highly recommended.[1] Support of dementia-caregiver dyads and respect for the autonomy of people with dementia in decision-making are main aspects of person-centred dementia care. However, ACP discussions are often deferred due to a lack of knowledge about dementia, limited awareness and support for ACP, and concerns about provoking negative emotions. This study aimed to promote ACP among people with early-stage dementia and their family caregivers in a community care setting in Hong Kong.

Methods

This was a multicentre, single-group, quasi-experimental, pretest-posttest study. A 3.5-hour ACP facilitator training session was provided to staff members of participating centres who then delivered the Have a Say (HAS) programme along with the research team. A set of ACP facilitator training materials and an ACP booklet were developed. Participating centres screened and invited potential participants who were Cantonese-speaking Chinese adults aged ≥55 years with early-stage dementia (stage 3 or 4 on the Global Deterioration Scale) and their designated family caregivers to participate on a dyadic basis.

The HAS programme was based on the Bandura's self-efficacy model and the shared decision-making model, designed to enhance self-efficacy and readiness for ACP among people with early-stage dementia and to support shared decision-making on future care among the dementia-caregiver dyad and healthcare professionals.[2,3] Details of the intervention have been reported elsewhere.[4]

The primary outcome was the ACP engagement level of participants with early-stage dementia. The secondary outcome was dyadic concordance regarding end-of-life care preferences. Outcomes were measured at baseline, immediately post-intervention, and 1-month post-intervention; they were analysed using generalised estimating equation models.

Results

In total, 124 staff members from 17 participating centres attended ACP facilitator training workshops. Among them, 29 (23.4%) delivered the HAS programme. Five (29.4%) of the 17 participating centres intended to integrate the HAS programme into their existing services.

Overall, 100 dyads of people with early-stage dementia (mean age, 78.5 years) and their caregivers (mean age, 64.6 years) were recruited from the 17 participating centres (Table 1). Among these dyads, 90% completed the HAS programme; attrition rates were 11% immediately post-intervention and 19% at 1-month post-intervention. Of the 89 dyads who completed the satisfaction survey, 77% of people with early-stage dementia and 83% of family caregivers reported satisfaction with the HAS programme.

TABLE 1. Characteristics of people with early-stage dementia and their family caregivers.

Characteristic	People with early-stage dementia (n=100)*	Caregivers (n=100)*
Sex		
Male	50 (50.0)	25 (25.0)
Female	50 (50.0)	75 (75.0)
Age, y	78.5±7.7 (55-96)	64.6±13.8 (24-89)
Marital status		
Married/cohabitated	72 (72.0)	75 (75.0)
Single	1 (1.0)	21 (21.0)
Widowed/separated/divorced	27 (27.0)	4 (4.0)
Education status		
Below primary	31 (31.0)	11 (11.0)
Primary	31 (31.0)	29 (29.0)
Secondary	33 (33.0)	40 (40.0)
Tertiary or above	5 (5.0)	20 (20.0)
Religion		
With	51 (51.0)	-
Without	49 (49.0)	-
Global Deterioration Scale score		
Stage 3	42 (42.0)	-
Stage 4	58 (58.0)	-
Living status		
Alone	11 (11.0)	-
With family members	89 (89.0)	-
Living status		
With care recipient	-	80 (80.0)
Not with care recipient	-	20 (20.0)
Relationship with care recipient		
Spouse	-	59 (59.0)
Child	-	40 (40.0)
Other	-	1 (1.0)
Working status		
Full-time	-	24 (24.0)
Part-time	-	7 (7.0)
Unemployed	-	69 (69.0)

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

In generalised estimating equation models, the overall ACP engagement score and subscale scores for 'self-efficacy' and 'readiness' significantly increased among people with early-stage dementia both immediately and at 1-month post-intervention relative to baseline (all P<0.001, Table 2). Participants reported completing fewer ACP behaviours that involved discussions with doctors and signing official documents than those that involved their medical decision-makers (Table 3). Dyadic concordance regarding end-of-life care preferences also significantly improved both immediately and at 1-month post-intervention (all P<0.001).

Discussion

The HAS programme was well accepted by dyads of people with early-stage dementia and their caregivers, with a high completion rate and satisfaction level. This may be attributed to the involvement of health and social care providers as ACP facilitators. The HAS programme emphasises a person-centred approach, allowing ACP facilitators to address participants' informational and emotional needs.

The attrition rate in this study was lower than the 17.8% at 1-month post-intervention and 34.3% at 6-month post-intervention from a previous study involving people nearing end of life in Hong Kong.[5] This is likely because participants in our study were relatively healthier. Earlier initiation of ACP is essential to ensure that patients can actively participate in the planning process.

The HAS programme significantly improved both self-efficacy and readiness for ACP among people with early-stage dementia. Nonetheless, most remained in the contemplation stage of ACP behaviours and had not yet planned or completed ACP actions, particularly those involving discussions with doctors or signing official documents. This may be attributed to the lack of healthcare services supporting completion of advance directives in the community, which could have hindered readiness to officially record medical decisions and end-of-life care preferences. Another possible explanation is that variability in life expectancy among people with early-stage dementia made it difficult to determine an appropriate time for ACP. The dyads may have uncertainty regarding end-of-life care decisions.[1] Therefore, behavioural changes beyond the contemplation stage may require additional guidance or resource support to facilitate ACP.

The results of this study highlight the importance of involving family caregivers in the ACP process. Dyadic concordance regarding end-of-life care preferences significantly improved over time, consistent with findings from a previous study that showed significant improvement at 6-month post-intervention.[5]

This study had some limitations. The absence of randomisation and a control group prevented confirmation of intervention effects from the HAS programme on ACP engagement and dyadic concordance regarding end-of-life care preferences. The use of convenience sampling may have introduced selection bias, limiting generalisation of the findings to individuals who actively engage with community care services. Participants may have

TABLE 2. Advance care planning (ACP) outcomes among people with early-stage dementia across three time points (n=100).

Outcome	Score*	Time effect β (95% confidence interval)	P value
Overall ACP engagement			
Baseline	1.44 (0.86)	-	-
Immediately post-intervention	2.65±0.83	1.07 (0.87-1.26)	<0.001
1-month post-intervention	2.53±0.89	0.94 (0.73-1.15)	<0.001
Self-efficacy subscale			
Baseline	2.20±1.23	-	-
Immediately post-intervention	3.61±0.99	1.42 (1.13-1.70)	<0.001
1-month post-intervention	3.42±1.13	1.24 (0.92-1.56)	<0.001
Readiness subscale			
Baseline	1.00 (0.17)	-	-
Immediately post-intervention	2.17±0.94	0.89 (0.69-1.09)	<0.001
1-month post-intervention	2.09±0.99	0.80 (0.57-1.03)	<0.001
Life Support Preferences Questionnaire			
Baseline	1.59±1.54	-	-
Immediately post-intervention	2.54±1.62	0.93 (0.56-1.31)	<0.001
1-month post-intervention	2.56±1.74	0.97 (0.56-1.38)	<0.001

* Data are presented as mean±standard deviation or median (interquartile range)

TABLE 3. Stages of change for each advance care planning (ACP) behaviour among people with early-stage dementia across three time points (n=100).

Stage of change	Baseline*	Immediately post-intervention*	1-month post-intervention*
1. Formally asking someone to be their medical decision maker			
Pre-contemplation: have never thought about it	74 (74.0)	20 (20.0)	28 (28.0)
Pre-contemplation: have thought about it, but not ready to do it	7 (7.0)	16 (16.0)	7 (7.0)
Contemplation: thinking about doing it in the next 6 months	1 (1.0)	0	1 (1.0)
Preparation: planning to do it in the next 30 days	0	0	0
Action: already done	18 (18.0)	51 (51.0)	44 (44.0)
2. Talking with their doctor about their preferred medical decision maker			
Pre-contemplation: have never thought about it	95 (95.0)	64 (64.0)	55 (55.0)
Pre-contemplation: have thought about it, but not ready to do it	2 (2.0)	16 (16.0)	21 (21.0)
Contemplation: thinking about doing it over the next few visits	1 (1.0)	2 (2.0)	1 (1.0)
Preparation: planning to do it at the next visit	0	2 (2.0)	1 (1.0)
Action: already done	2 (2.0)	3 (3.0)	3 (3.0)
3. Signing official papers to name their medical decision maker			
Pre-contemplation: have never thought about it	96 (96.0)	63 (63.0)	57 (57.0)
Pre-contemplation: have thought about it, but not ready to do it	3 (3.0)	15 (15.0)	13 (13.0)
Contemplation: thinking about doing it in the next 6 months	0	2 (2.0)	2 (2.0)
Preparation: planning to do it in the next 30 days	1 (1.0)	0	1 (1.0)
Action: already done	0	7 (7.0)	8 (8.0)
4. Talking to their decision maker about their end-of-life medical care			
Pre-contemplation: have never thought about it	82 (82.0)	24 (24.0)	31 (31.0)
Pre-contemplation: have thought about it, but not ready to do it	6 (6.0)	8 (8.0)	9 (9.0)
Contemplation: thinking about doing it in the next 6 months	0	0	2 (2.0)
Preparation: planning to do it in the next 30 days	0	1 (1.0)	2 (2.0)
Action: already done	12 (12.0)	54 (54.0)	37 (37.0)

* Data are presented as No. (%) of participants

TABLE 3. (cont'd)

Stage of change	Baseline*	Immediately post-intervention*	1-month post-intervention*
5. Talking to their doctor about their end-of-life medical care			
Pre-contemplation: have never thought about it	95 (95.0)	68 (68.0)	56 (56.0)
Pre-contemplation: have thought about it, but not ready to do it	2 (2.0)	15 (15.0)	24 (24.0)
Contemplation: thinking about doing it over the next few visits	0	0	0
Preparation: planning to do it at the next visit	1 (1.0)	2 (2.0)	1 (1.0)
Action: already done	2 (2.0)	2 (2.0)	0
6. Signing official papers to document their end-of-life medical care preferences			
Pre-contemplation: have never thought about it	97 (97.0)	62 (62.0)	57 (57.0)
Pre-contemplation: have thought about it, but not ready to do it	2 (2.0)	15 (15.0)	12 (12.0)
Contemplation: thinking about doing it in the next 6 months	0	3 (3.0)	1 (1.0)
Preparation: planning to do it in the next 30 days	1 (1.0)	0	2 (2.0)
Action: already done	0	8 (8.0)	9 (9.0)

been better prepared for ACP or less opposed to it. The dyadic nature of the study also excluded those without family support. Follow-up assessments were conducted via telephone, which may have influenced participants' responses by their partners.

Conclusion

The substantial involvement of participating centres and frontline healthcare professionals suggests interest in integrating the HAS programme into existing services. Regular ACP training should be provided to frontline health and social care staff, in collaboration with doctors, to facilitate the completion of advance directives and discussions regarding documented care preferences across various healthcare settings.

Funding

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Glass ionomer sealant versus fluoride varnish in preventing occlusal caries among preschool children: a randomised controlled trial (abridged secondary publication)

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KEY MESSAGES

1. Both the quarterly application of sodium fluoride varnish and a single placement of glass ionomer sealant were equally effective in preventing occlusal caries in primary second molars over 24 months.
2. Placement of glass ionomer sealant was more cost-effective in preventing occlusal caries within 24 months.
3. Caries experience and incipient occlusal lesions increased the likelihood of caries progression into dentine in primary second molars.

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Introduction

Early childhood caries affects preschool children worldwide. The occlusal surface of primary molars is highly susceptible to caries. Fluoride varnish (FV) and fissure sealants are effective in preventing occlusal caries in primary molars. FV inhibits caries in both primary and permanent teeth[1] and requires reapplication every 3 to 6 months. Fissure sealants prevent occlusal caries in permanent molars. Resin-based sealants and glass ionomer sealants (GISs) act as barriers by sealing occlusal pits and fissures, thus reducing plaque retention. GISs also release fluoride over time, providing additional caries prevention for both treated and adjacent teeth. A Cochrane review found that fissure sealants were more effective than FV in preventing caries in permanent molars.[1] Fissure sealants have shown effectiveness in permanent molars among school-aged children.[2] However, fissure sealant application in younger children is technique-sensitive. GIS can bond to enamel and is moisture-tolerant, making it suitable for use in young patients and in outreach settings. This study aimed to determine the relative effectiveness and costs of sodium FV and GIS in preventing occlusal caries in the primary molars of preschool children.

Methods

Preschool children from 16 kindergartens were invited to participate. They were examined by a calibrated dentist using the Visible Plaque Index, dmft (the number of decayed, missing due to caries, and filled teeth), and ICDAS (International Caries Detection and Assessment System) scores. Participants were randomly assigned to receive either sodium FV or GIS. Oral health behaviours, dental history, and socioeconomic background were recorded via questionnaire. Children in the sodium FV group were recalled at months 3, 6, 9, 12, 15, 18, 21, and 24 for reapplication. Follow-up examinations were conducted at months 6, 12, 18, and 24 by the same examiner. A 10% random sample was re-examined to assess reproducibility. Sealant retention and caries development in primary second molars (PSMs) were evaluated.

Results

In total, 413 eligible children were included in the analysis. They were randomly assigned to either the sodium FV group (n=228, 845 PSMs) or the GIS group (n=185, 665 PSMs). Overall, 112 PSMs were excluded due to existing caries, prior restorations, partial eruption, non-compliance, strong gag reflex, or difficulty in achieving a dry field. Dropout rates at various intervals did not significantly differ between groups. Children more likely to be lost to follow-up at 24 months were older ($P<0.001$), had older parents ($P=0.018$), and came from higher-income households ($P<0.001$).

Cohen's kappa values for intra-examiner reliability were 0.774 for the Visible Plaque Index, 0.964 for dmft, and 0.834 for ICDAS II scores. At 24 months, caries development on the occlusal surface was observed in 18.3% of the sodium FV group and

17.7% of the GIS group. Of all PSMs, 22.3% and 20.7% developed dentinal caries in the respective groups. The two groups were comparable in terms of occlusal caries prevention (Table 1). GIS survival rates declined over time, reaching 4.4% at 24 months. Partial GIS retention resulted in dentinal caries in 1% of molars at 24 months. Dislodged GIS led to dentinal caries in 5.1%, 13.6%, 11.1%, and 16.7% of molars at 6, 12, 18, and 24 months, respectively (Table 2). Regression analyses showed that incipient occlusal caries lesions and higher baseline dmft scores significantly increased the likelihood of developing dentinal caries after 24 months. The overall direct costs for delivering sodium FV and GISs in kindergarten settings were HK$61.9 and HK$28.0 over 24 months, respectively. GIS was significantly less costly over 24 months.

Discussion

Both a single placement of GIS and quarterly application of sodium FV were effective in preventing occlusal caries in PSMs after 24 months. GIS placement was significantly less costly; however, GIS retention rates among preschool children were low at 24 months, limiting the effectiveness of occlusal caries prevention. This low retention rate may be attributed to shallow fissures, low compliance, and difficulties in achieving a dry field. The viscosity of GISs affect their clinical efficacy and retention. High-viscosity GISs may perform better. The present study used a medium-viscosity GIS, which may not be ideal for young children in outreach settings.

The present study did not implement measures to improve children's oral hygiene, which may explain the continued progression of dental caries despite preventive interventions. In Hong Kong, preschool children have access to fluoridated water and toothpaste; therefore, additional benefits from sodium FV and GIS may be limited. The importance of oral health education before implementing interventions is emphasised because baseline caries experience and early signs of decay are key factors for caries development.

Few studies have compared the cost-effectiveness of sealants and FV.[3,4] GIS appears more favourable because of a single application. However, its low retention rates diminishes its cost-effectiveness. In China, sealants yield similar caries prevention outcomes at 24 months but are associated with higher costs.[3] In Brazil, sealants are more cost-effective at 24 months but not at 48 months for high-risk children.[4] Providers may consider integrating FV application with infant vaccination schedules to reduce indirect dental and opportunity costs. In Thailand, such integration significantly improves the cost-effectiveness of FV.[5] The cost of applying sodium FV could also be reduced by involving dental hygienists or dental therapists rather than dentists. Further research is needed to better understand the cost-effectiveness of sealants compared with FV.

Conclusion

Quarterly application of sodium FV and single-placement GIS demonstrated similar efficacy in preventing occlusal caries in PSMs over 24 months; the GIS was less expensive. Baseline caries status and incipient occlusal caries were associated with an increased risk of occlusal caries progression in PSMs.

Funding

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TABLE 1. Incidence of dentinal caries on the occlusal surfaces and all surfaces of primary second molars (PSMs) over 24 months.

Dentinal caries	Baseline (n=1510)*		6 months (n=1170)*		12 months (n=1282)*		18 months (n=712)*		24 months (n=698)*		Intragroup comparisons	
On occlusal surfaces (ICDAS score ≥4)												
All included PSMs	n=1510	0	n=1170	70 (6.0)	n=1282	171 (13.3)	n=712	81 (11.4)	n=698	126 (18.1)	n=509	P<0.001
Sodium fluoride varnish	n=845	0	n=676	47 (7.0)	n=721	91 (12.6)	n=405	66 (16.3)	n=404	74 (18.3)	n=291	P<0.001
Glass ionomer sealant	n=665	0	n=494	27 (5.5)	n=561	80 (14.3)	n=307	38 (12.4)	n=294	52 (17.7)	n=218	P<0.001
		-		P=0.302		P=0.392		P=0.143		P=0.831		
On PSM (ICDAS score ≥4)												
All included PSMs	n=1510	0	n=1170	96 (8.2)	n=1282	217 (16.9)	n=712	133 (18.7)	n=698	151 (21.6)	n=509	P<0.001
Sodium fluoride varnish	n=845	0	n=676	60 (8.9)	n=721	118 (16.4)	n=405	81 (20.0)	n=404	90 (22.3)	n=291	P<0.001
Glass ionomer sealant	n=665	0	n=494	36 (7.3)	n=561	99 (17.6)	n=307	52 (16.9)	n=294	61 (20.8)	n=218	P<0.001
		-		P=0.328		P=0.544		P=0.299		P=0.612		

Abbreviation: ICDAS=International Caries Detection and Assessment System

* Data are presented as No. (%) of PSMs unless otherwise indicated

TABLE 2. Glass ionomer sealant retention and caries occurrence on the occlusal surfaces of primary second molars (PSMs) over 24 months.

Outcome	Tooth 55*	Tooth 65*	Tooth 75*	Tooth 85*	All included PSMs*	P value (sealant retention)	P value (caries occurrence)
6 months	n=123	n=122	n=125	n=124	n=494	0.246	0.653
Sealant lost without caries	98 (79.7)	100 (82.0)	86 (68.8)	92 (74.2)	376 (76.1)		
Sealant retained fully or partially without caries	21 (17.1)	15 (12.3)	31 (24.8)	24 (19.4)	91 (18.4)		
Sealant retained fully or partially with dentinal caries	0	0	1 (0.8)	1 (0.8)	2 (0.4)		
Decayed with dentinal caries or filled	4 (3.3)	7 (5.7)	7 (5.6)	7 (5.7)	25 (5.1)		
12 months	n=139	n=139	n=143	n=140	n=561	0.008	0.951
Sealant lost without caries	115 (82.7)	133 (81.3)	104 (72.7)	112 (80.0)	444 (79.1)		
Sealant retained fully or partially without caries	4 (2.9)	8 (5.8)	17 (11.9)	8 (5.7)	37 (6.6)		
Sealant retained fully or partially with dentinal caries	0	0	4 (2.8)	0	4 (0.7)		
Decayed with dentinal caries or filled	20 (14.4)	18 (13.0)	18 (12.6)	20 (14.3)	76 (13.6)		
18 months	n=76	n=75	n=77	n=79	n=307	0.003	0.329
Sealant lost without caries	65 (85.5)	62 (82.7)	60 (77.9)	64 (81.0)	251 (81.8)		
Sealant retained fully or partially without caries	1 (1.3)	2 (2.7)	12 (15.6)	3 (3.8)	18 (5.9)		
Sealant retained fully or partially with dentinal caries	1 (1.3)	1 (1.3)	2 (2.6)	0	4 (1.3)		
Decayed with dentinal caries or filled	9 (11.8)	10 (13.3)	3 (3.9)	12 (15.2)	34 (11.1)		
24 months	n=73	n=72	n=73	n=76	n=294	0.039	0.990
Sealant lost without caries	61 (83.6)	59 (81.9)	53 (72.6)	59 (77.6)	232 (78.9)		
Sealant retained fully or partially without caries	0	0	7 (9.6)	3 (4.0)	10 (3.4)		
Sealant retained fully or partially with dentinal caries	0	1 (1.4)	2 (2.7)	0	3 (1.0)		
Decayed with dentinal caries or filled	12 (16.4)	12 (16.7)	11 (15.1)	14 (18.4)	49 (16.7)		

* Data are presented as No. (%) of PSMs

Government (#16172221). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

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Optimal age groups to target for influenza vaccination to reduce the impact of influenza in Hong Kong: abridged secondary publication

TK Tsang *, BJ Cowling

KEY MESSAGES

1. Based on the fitted directed graph model, the probabilities of infection among household members of vaccinated and unvaccinated children were similar, suggesting limited indirect protection for household members through vaccination of children.
2. Influenza vaccination strategies targeting the age group with the highest attack rate are most effective. Children have the highest attack rate; therefore, influenza vaccination strategies targeting children can decrease the attack rate in older adults.
3. Influenza vaccination strategies targeting children are more efficient in most influenza seasons. However, attack rate and infection severity in older adults should also be considered.

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Introduction

Influenza viruses cause considerable morbidity and mortality each year. Vaccination against influenza is the most effective measure to control its spread. Influenza vaccination strategies typically target high-risk populations such as children aged <2 years, older people aged ≥65 years, individuals with chronic diseases, and pregnant women. However, mathematical models suggest that vaccination strategies targeting children are optimal in certain transmission scenarios. Vaccination as a household-level intervention can indirectly protect other family members. In Hong Kong, the risk of infection for unvaccinated members of a household with one vaccinated child was reduced by only 5%, despite a direct vaccine efficacy of 70% during the 2010 influenza B epidemic.[1]

This study aimed to explore age-specific strategies for family-level interventions (to reduce the risk of infection in unvaccinated family members) and population-level interventions (to reduce the risk of infection in non-target age groups).

Methods

Participants were recruited from two community-based randomised controlled trials to evaluate the direct and indirect benefits of influenza vaccination.[2,3] In the subsequent observational follow-up from late 2010 to late 2013, serum specimens were collected from all participants each autumn (October to December) and from 25% of participants each spring (April to May).[4] Sera were tested against influenza A(H1N1)pdm09 and A(H3N2)-like viruses for each study year, using haemagglutination inhibition assays.[1] Syndromic surveillance data in Hong Kong were used to identify influenza epidemics.

Our previous directed graph model, which estimated the probability of infection from both community and household transmission during the epidemic, was able to overcome the difficulty of using serological data with only final infection status for each participant, given unobserved transmission chains.[1,5] Two scenarios were simulated to estimate the degree of indirect protection provided by influenza vaccination. First, one child in each household was vaccinated. Second, all children in each household were vaccinated. We simulated 10 000 epidemics for each scenario with 150 000 households. In each simulation, we constructed corresponding digraphs to identify the source of each infection and estimate the probability of infection from both the community and households. The indirect protection of a vaccine strategy was estimated by the ratio of the probability of infection in a group to the corresponding probability of infection under a no-vaccination strategy.

To model vaccine strategies targeting different age groups, we used an age-structured susceptible-exposed-infected-recovered model. The model was stratified according to age group (0-17, 18-49, 50-64, and ≥65 years) and vaccination status. We then estimated model parameters using the attack rates from three influenza epidemics between 2009 and 2013. The following strategies were tested: baseline coverage, increasing coverage by 20% or 40% in the age group of ≥65 years (older adults), increasing coverage by 20% or 40% in the age group of 0 to 17

years (children), and increasing coverage by 20% or 40% in both age groups. Population size and vaccine coverage were extracted from the literature. We investigated the indirect protection provided to other age groups by vaccinating the high-transmissibility age group (0-17 years). Effectiveness was estimated by comparing the cumulative incidences of infections under different vaccine strategies with the incidence under baseline coverage.

Results

Ten rounds of sera were collected between 2009 and 2013 during six major influenza A epidemics, including a pH1N1 outbreak in 2009, two pH1N1 epidemics in 2011 and 2013, and three H3N2 epidemics in 2010, 2012, and 2013 (Fig 1).

Overall, we recruited 829 households across two trials; 86 households participated in both trials. Finally, 2512 participants were included during the pH1N1 pandemic outbreak, and 1443 to 1943 participants were included in each of the other five epidemics, after exclusion of households without complete infection status for all members.

Based on the fitted directed graph model, two strategies were simulated: vaccinating one child in each household and vaccinating all children in the household (Fig 2). In the optimal scenario, where the direct vaccine efficacy was 70%, the probability of household infection for unvaccinated adult contacts was almost halved under both strategies, compared with no vaccination. Relative probabilities ranged from 0.62 to 0.68 and 0.44 to 0.54, respectively, across the six epidemics. However, the reduction in total probability of infection was marginal because the community was the main source of infection. These relative probabilities ranged from 0.93 to 0.96 and 0.91 to 0.94, respectively.

The degree of indirect protection from vaccinating children depended on the attack rate (Table). Assuming vaccine efficacy was 60% and vaccine coverage increased by 40%, in an influenza season with a high attack rate (season 1), the attack rates for children and older adults could be reduced by 31% and 48%, respectively. When targeting only children, the attack rates for children and older adults could be reduced by 50% and 39%, respectively. These findings suggest that indirect protection from increasing vaccine coverage is greater in children than in older adults. When increasing coverage of both children and older adults by 20%, the attack rates could be further reduced by 38% and 43%, respectively. Compared with allocating all vaccines to children (coverage increased by 40%), concurrently allocating vaccines to both children and older adults (coverage increased by 20% for both age groups) reduced the attack rates by 12% less in children and 4% more in older adults. Similar patterns were observed in simulations for season 4 or when only coverage of the targeted group was increased by 20%. During season 3, the attack rate remained highest in children, but the difference in attack rates between children and older adults was smaller (0.07). Therefore, targeting children or targeting older adults brings similar indirect protection to other age groups.

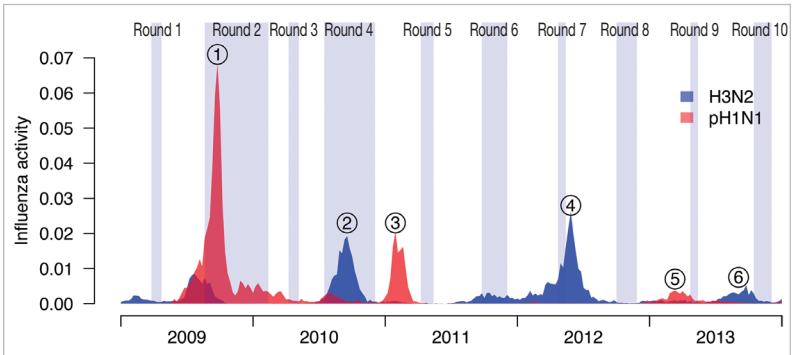

FIG 1. Influenza activity from 2009 to 2013, including six epidemic seasons and 10 rounds of sera collection.

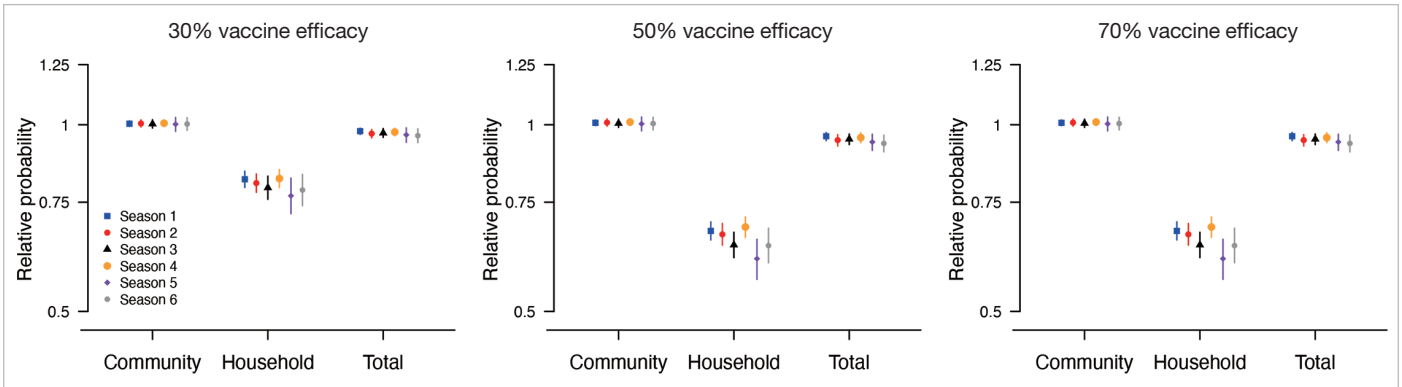

FIG 2. Relative infection probabilities (from the community, infected household members, or both) during the six epidemic seasons for household contacts of vaccinated children when all children in the household are vaccinated (strategy 2), compared with no vaccination of children. Results are shown for assumed vaccine efficacies of 30%, 50%, and 70%.

TABLE. Estimated attack rates across five influenza seasons (season 5 cannot be calibrated owing to 0 observed attack rate in older adults) under various vaccine strategies when vaccine efficacy is set to be 60%.

Strategy	Attack rate				Vaccine efficacy, %			
	Age group 0-17 y (children)	Age group 18-50 y	Age group 51-64 y	Age group ≥65 y (older adults)	Age group 0-17 y (children)	Age group 18-50 y	Age group 51-64 y	Age group ≥65 y (older adults)
Season 1 (high attack rate)								
Baseline coverage	0.403	0.115	0.066	0.205				
Increase coverage by 20% in age group ≥65 y	0.349	0.096	0.055	0.151	13	17	17	26
Increase coverage by 40% in age group ≥65 y	0.278	0.078	0.045	0.107	31	32	32	48
Increase coverage by 20% in age group 0-17 y	0.293	0.089	0.051	0.162	27	23	23	21
Increase coverage by 40% in age group 0-17 y	0.202	0.067	0.038	0.125	50	42	42	39
Increase coverage by 20% in age groups 0-17 y and ≥65 y	0.248	0.072	0.041	0.117	38	37	38	43
Increase coverage by 40% in age groups 0-17 y and ≥65 y	0.138	0.043	0.024	0.062	66	63	64	70
Season 2 (high attack rate)								
Baseline coverage	0.099	0.101	0.098	0.316				
Increase coverage by 20% in age group ≥65 y	0.067	0.068	0.066	0.199	32	33	33	37
Increase coverage by 40% in age group ≥65 y	0.044	0.044	0.043	0.115	56	56	56	64
Increase coverage by 20% in age group 0-17 y	0.082	0.095	0.092	0.300	17	6	6	5
Increase coverage by 40% in age group 0-17 y	0.066	0.089	0.086	0.285	33	12	12	10
Increase coverage by 20% in age groups 0-17 y and ≥65 y	0.055	0.063	0.062	0.187	44	38	37	41
Increase coverage by 40% in age groups 0-17 y and ≥65 y	0.029	0.038	0.037	0.101	71	62	62	68
Season 3 (high attack rate)								
Baseline coverage	0.159	0.136	0.120	0.088				
Increase coverage by 20% in age group ≥65 y	0.143	0.122	0.107	0.068	10	10	11	23
Increase coverage by 40% in age group ≥65 y	0.129	0.109	0.095	0.051	19	20	21	42
Increase coverage by 20% in age group 0-17 y	0.126	0.120	0.106	0.078	21	12	12	11
Increase coverage by 40% in age group 0-17 y	0.098	0.106	0.093	0.068	38	22	23	23
Increase coverage by 20% in age groups 0-17 y and ≥65 y	0.113	0.108	0.095	0.059	29	21	21	33
Increase coverage by 40% in age groups 0-17 y and ≥65 y	0.079	0.084	0.074	0.039	50	38	38	56
Season 4 (high attack rate)								
Baseline coverage	0.273	0.232	0.270	0.084				
Increase coverage by 20% in age group ≥65 y	0.260	0.220	0.256	0.068	5	5	5	19
Increase coverage by 40% in age group ≥65 y	0.247	0.208	0.244	0.054	10	10	10	36
Increase coverage by 20% in age group 0-17 y	0.217	0.207	0.242	0.074	21	11	10	12
Increase coverage by 40% in age group 0-17 y	0.169	0.183	0.216	0.065	38	21	20	23
Increase coverage by 20% in age groups 0-17 y and ≥65 y	0.207	0.196	0.23	0.060	24	16	15	29
Increase coverage by 40% in age groups 0-17 y and ≥65 y	0.152	0.163	0.193	0.042	44	30	29	50
Season 6 (high attack rate)								
Baseline coverage	0.077	0.057	0.093	0.091				
Increase coverage by 20% in age group ≥65 y	0.067	0.048	0.08	0.061	13	16	14	33
Increase coverage by 40% in age group ≥65 y	0.058	0.041	0.069	0.045	25	28	26	51
Increase coverage by 20% in age group 0-17 y	0.063	0.052	0.086	0.075	18	9	8	18
Increase coverage by 40% in age group 0-17 y	0.052	0.048	0.079	0.069	32	16	15	24
Increase coverage by 20% in age groups 0-17 y and ≥65 y	0.055	0.044	0.074	0.056	29	23	20	38
Increase coverage by 40% in age groups 0-17 y and ≥65 y	0.040	0.035	0.058	0.039	48	39	38	57

In influenza seasons where attack rates were comparable between older adults and children, or the attack rate in older adults was higher (eg, season 6), the attack rates in children and older adults could be reduced by 25% and 51%, respectively, if increasing vaccine coverage for older adults by 40%. When targeting only children, the attack rates in children and older adults could be reduced by 32% and 24%, respectively. In such scenarios, increasing vaccine coverage in older adults (rather than children) would be more beneficial.

Discussion

We studied the transmission dynamics of influenza A virus within households during six epidemics from 2009 to 2013 in Hong Kong to identify factors that influence transmission. We then assessed the indirect benefits of vaccinating children in households, based on different levels of vaccine efficacy. Although vaccination reduced the probability of transmission within households, its impact on the overall probability of infection for household contacts was small. Similar to our previous study on influenza B epidemics,[1] household transmission was estimated to represent approximately 10% of all transmission events during the six influenza A epidemics—lower than the 30% previously reported. This proportion could be due to higher rates of community transmission in Hong Kong, potentially because of crowded public transport and schools. Vaccine coverage in Hong Kong was low; therefore, our results should be assumed to reflect only indirect protection at the household level.

Vaccinating the age group with the highest attack rate would provide greater protection across all age groups. The attack rate was highest in children during most influenza seasons. Therefore, targeting children could provide indirect protection in most seasons, regardless of whether vaccine coverage is increased in children or older adults. Our results support implementing a transmission-limiting strategy in Hong Kong: targeting children was more effective because it could reduce the attack rate in children and thus indirectly reduce the attack rate and mortality in older adults.

However, when deciding which age group to target for vaccination, the mortality rate in older adults should also be considered. For example, when an influenza variant is associated with increased severity among older adults, vaccination of this group may remain a priority. Similarly, if a variant is more likely to infect older adults, the targeted age group should be shifted accordingly. Therefore, attack and mortality rates in older adults should be closely monitored to determine whether a modified vaccination strategy is warranted.

To estimate household transmission dynamics, we relied on a ≥4-fold rise in antibody titre to identify influenza virus infections, which may have resulted in measurement error. Our model did not explicitly include contact rates among age groups; therefore, it may have underestimated the impact of vaccine strategies targeting children.

Conclusion

Targeting children may not provide indirect protection to other household members. Individual vaccination remains crucial for protection against influenza at the household level. At the population level, targeting children is likely to be the optimal strategy because the attack rate is highest in children during most seasons. However, the severity of circulating strains in older adults should also be considered. Close monitoring of attack rates across age groups is essential to determine which age group should be prioritised for increased vaccine coverage.

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Disclosure

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1. Tsang TK, Wang C, Fang VJ, et al. Indirect protection from vaccinating children against influenza A virus infection in households. Viruses 2022;14:2097.

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Rat hepatitis E virus and genotype 4 hepatitis E virus infections among immunocompromised persons and patients with hepatitis in Hong Kong: abridged secondary publication

S Sridhar *, CCY Yip, PCY Woo, KY Yuen

KEY MESSAGES

1. Rat hepatitis E virus is a major cause of hepatitis E among transplant recipients and immunocompromised patients in Hong Kong.
2. Most of these infections belong to a single strain group: LCK-3110.
3. Street rats in Hong Kong commonly harbour rat hepatitis E virus, although few carry LCK-3110-like strains associated with most human disease.
4. Both rat and genotype 4 hepatitis E virus variants frequently progress to chronicity in immunocompromised persons with poor response to immunosuppression reduction alone.
5. Chronic rat hepatitis E is curable with ribavirin; the genetic basis for non-susceptibility to ribavirin in genotype 4 hepatitis E virus is substantially different from genotype 3 hepatitis E virus.

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Introduction

Hepatitis E virus (HEV) is one of the most common causes of acute viral hepatitis in Hong Kong. HEV variants capable of infecting humans include swine HEV (HEV-A genotypes 3 and 4) and rat hepatitis E virus (HEV-C). These are the most common causes of hepatitis E in Hong Kong.[1,2] Infection with HEV-A genotype 3 is well studied in terms of rates of progression to chronicity and responses to ribavirin.[3] However, it is uncertain how humans acquire HEV-C infections from rats. Genomic epidemiological links between rat and human HEV-C strains are not well defined. We compared HEV-A and HEV-C infection prevalences among patients with hepatitis and transplant recipients in Hong Kong and in immunocompromised patients. Rates of HEV-C carriage in captured street rats were estimated.

Methods

Blood samples from patients with hepatitis and transplant recipients, along with rectal swabs from captured street rats, were tested for HEV-C RNA and/or HEV-A RNA. Some transplant recipients also provided 1-year follow-up samples; these were retrieved for HEV RNA screening and HEV immunoglobulin G testing to identify cases of asymptomatic seroconversion and subclinical infection. Sequencing was performed for human and rat HEV isolates, followed by phylogenetic analysis. Clinical characteristics of HEV-A genotype 4 and HEV-C infections in immunocompromised persons were compared.

Results

In total, six cases of HEV-C infection and 17 cases of HEV-A infection were identified among transplant recipients and patients with hepatitis. All six cases of HEV-C infection occurred in immunocompromised persons, whereas only five cases of HEV-A infection occurred in immunocompromised persons.

Between January 2016 and December 2020 in Hong Kong, 21 immunocompromised patients were infected with HEV-A genotype 4 (n=12) and/or HEV-C (n=13) [Table]. Both HEV-A genotype 4 and HEV-C active infections in immunocompromised persons frequently progressed to chronicity requiring antiviral therapy. Ribavirin generally achieved a good response in HEV-C infections. Ribavirin-refractory HEV-A genotype 4 infections were linked to mutations such as K1383N in the RNA-dependent RNA polymerase segment of the HEV genome, which was documented in all such patients. Most human HEV-C infections were due to a single strain group—LCK-3110—although infections from other strain groups were also documented, with diverse clinical phenotypes such as prolonged infection in the absence of immunosuppression.

Of 1161 street rats in Hong Kong, 72 (6.2%) had

detectable HEV-C RNA, but only two of these were confirmed to carry the LCK-3110 strain group. One of these rats was captured in Wong Tai Sin and the other in Wan Chai. A correlation between HEV-C epizootics and human infection was not established, although this could be due to the sporadic nature of sampling.

Discussion

HEV-C is an important cause of hepatitis E infection in transplant recipients and immunocompromised patient groups in Hong Kong. Most of these infections belong to a single strain group. Street rats in Hong Kong commonly harbour HEV-C, although few carry the LCK-3110-like strains associated with most human cases. Both HEV-C and HEV-A genotype 4 variants frequently progress to chronicity in immunocompromised persons with poor response to immunosuppression reduction. Chronic HEV-C infection is curable with ribavirin; the genetic basis for non-susceptibility to ribavirin for HEV-A genotype 4 is substantially different from HEV-A genotype 3.

Clinicians should test for HEV-C in hepatitis patients in Hong Kong, particularly in immunocompromised individuals. Immunosuppression reduction alone seldom resolves HEV-C infection in immunocompromised hosts, but oral ribavirin is an effective treatment.

Carriage of HEV-C was observed among captured street rats in Hong Kong, although no evidence was found for an active epizootic of the same HEV-C strain group causing human disease. Continued genomic surveillance and sequencing of HEV-C in rats and humans is required.

TABLE. Clinical characteristics of 21 immunocompromised patients infected with hepatitis E virus (HEV)-A genotype 4 and/or HEV-C.

Characteristic	Patients with HEV-A genotype 4 (n=12)*	Patients with HEV-C (n=13)*
Male sex	9 (75.0)	11 (84.6)
Mean age, y	52.8	54.9
Immunosuppressive condition		
Liver transplant	1 (8.3)	2 (15.4)
Kidney transplant	6 (50.0)	5 (38.5)
Heart transplant	1 (8.3)	1 (7.7)
Lung transplant	1 (8.3)	0
Haematopoietic stem cell transplant	1 (8.3)	1 (7.7)
Haematological malignancy	2 (16.7)	1 (7.7)
Advanced HIV	0	2 (15.4)
Rheumatic disorder	0	1 (7.7)
Hepatitis E outcomes		
Spontaneous resolution	0	1 (7.7)
Early ribavirin with sustained virological response	2 (16.7)	2 (15.4)
Persistent infection	10 (83.3)	10 (76.9)
Persistent hepatitis E	n=10	n=10
Death before treatment	2 (20.0)	3 (30.0)
Resolved with reduced immunosuppression	1 (10.0)	0
Sustained virological response on ribavirin	4 (40.0)	4 (40.0)
Ribavirin non-responder	2 (20.0)	0
Responsive without sustained virological response	1 (10.0)	3 (30.0)

* Data are presented as No. (%) of participants unless otherwise indicated

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Disclosure

The results of this research have been previously published in:

1. Sridhar S, Yip CCY, Lo KHY, et al. Hepatitis E virus species C infection in humans, Hong Kong. Clin Infect Dis 2022;75:288-96.
2. Sridhar S, Situ J, Cai JP, et al. Multimodal investigation of rat hepatitis E virus antigenicity: implications for infection, diagnostics, and vaccine efficacy. J Hepatol 2021;74:1315-24.
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Human cytomegalovirus latent genes facilitating human immunodeficiency virus type 1 coinfection in CD34+ cells: abridged secondary publication

WK Lee, Z Ye, AKL Cheung *, Z Chen, H Wang

KEY MESSAGES

1. Latent infection of human cytomegalovirus (HCMV) in CD34+ progenitor cells modulates the innate STING immune pathway.
2. Although the STING pathway remains active, the critical step of p-IRF3 translocation required to initiate type-I IFN expression is impaired.
3. This impairment inhibits the differentiation of CD34+ progenitor cells into immune-activating myeloid cells, thus promoting viral persistence.
4. HCMV infection of early CD34+ progenitor cells facilitates HIV-1 coinfection.
5. Detection of HCMV in urine enables early prognosis and prediction of end-organ diseases in HIV-1 patients.

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Introduction

Human cytomegalovirus (HCMV) is a ubiquitous betaherpesvirus that infects 60% to 90% of the global population. The virus establishes lifelong latent infection in CD34+ haematopoietic stem and progenitor cells (HSPCs) and myeloid lineage cells in the human host. It remains asymptomatic unless immune surveillance is impaired, as observed in immunocompromised HIV-1 patients or immunosuppressed transplant recipients. However, the persistence of latent HCMV is an underlying factor in the development of post-transplant organ pathogenesis (eg, hepatitis and pneumonia), congenital conditions (eg, biliary atresia), autoimmune diseases, and the phenomenon of immune memory inflation.

A critical aspect of HCMV latency involves the impairment of differentiation in latently infected CD34+ HSPCs. These progenitor cells can generate innate immune responses or differentiate into antigen-presenting cells such as dendritic cells, which can induce antiviral adaptive immune responses. HCMV latency inhibits the differentiation of HSPCs through various mechanisms. For instance, the latent gene *LAcmvIL-10* suppresses pro-inflammatory cytokines and prevents latently infected myeloid progenitor cells from differentiating into dendritic cells.[1] Latently expressed miRNAs, such as miR-US5-2, target the transcriptional repressor NGFI-A binding protein 1 and upregulate transforming growth factor-β expression, resulting in myelosuppression. HCMV also modulates signal transducer and activator of transcription 3 activity to induce HSPC differentiation into an immunosuppressive monocyte subset, which produces high levels of nitric oxide to facilitate latency.[2] Acute and chronic exposure to type-I interferons (IFNs) can influence the maintenance of haematopoiesis. Innate immune activation regulates haematopoiesis in CD34+ cells through the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway and autocrine type-I IFNs.[3] Moreover, the bacterial second messenger c-di-GMP binds and activates the STING pathway to modulate HSPC homeostasis through type-I IFNs. However, the effect of HCMV latent infection on type-I IFN expression and its influence on CD34+ HSPC differentiation remain poorly understood.

Among immunocompromised HIV-1-infected individuals, HCMV can be reactivated in patients with advanced, stage 4 HIV/AIDS (ie, when the CD4 count is <200 cells/mm^3), leading to multiple end-organ diseases (EODs) and mortality, particularly in the absence of antiretroviral therapy. HCMV-seropositive individuals infected with HIV-1 progress to AIDS approximately 30 months faster and exhibit a more aggressive disease course than HCMV-seronegative patients.[4] There is an association between HCMV DNA and HIV RNA concentrations in peripheral blood and manifestation of serious EODs including retinitis, colitis, hepatitis, and pneumonitis. This illustrates the implications of latent HCMV pathogenesis in HIV-1-infected patients. HCMV and HIV-1 may interact synergistically within CD34+ progenitor stem cells through unknown mechanisms.[5]

HCMV can increase HIV-1 pathogenicity by post-transcriptionally activating proviral HIV-1 DNA or by inducing inflammatory responses that trigger virulent HIV-1 gene expression. The detection of HCMV serves as a predictor of EODs and is associated with a 40% to 60% increased risk of developing EODs in HIV-1-infected individuals. The reactivation of latent HCMV in HIV-1-infected patients may attribute to the onset of EODs. Although associations between plasma HCMV DNA and EODs in stage 4 HIV-1 infection have been reported, there are limited data regarding HCMV in urine and its prognostic value during the early stages of HIV-1 infection.

This study aimed to determine how HCMV latent infection increases its persistence in CD34$^+$ cells and to evaluate the potential of HCMV as a prognostic marker for EOD risk in HIV-1-infected patients.

Results

Latent HCMV impairs type-I IFN-induced CD34$^+$ cell differentiation

We first examined the effect of type-I IFNs (ie, IFN-β) on CD34$^+$ cell differentiation. Flow cytometric analysis revealed that IFN-β at concentrations of 1000 or 3000 U/mL increased the frequencies of CD38$^+$ cells among CD34$^+$ cells, accompanied by an increase in myeloid progenitor subsets including common dendritic cell progenitors, common myeloid progenitors, and granulocyte-monocyte progenitors (Fig 1). In contrast, the frequencies of early progenitor subsets such as haematopoietic stem cells and multipotent progenitors decreased. Stimulation of the cells with 2′3′-cGAMP activated the STING pathway and downstream IFN-β production, modestly increasing the myeloid subsets by day 7 post-treatment. These findings indicate that IFN-β can induce myelopoiesis in the CD34$^+$ cell model and suggest that cell differentiation is suppressed in the presence of latent HCMV infection.

To determine whether differentiation is inhibited in HCMV^{GFP-} cells due to viral modulation of type-I IFNs during latency, we measured expression and secretion levels of IFN-α and IFN-β in both mock-infected and HCMV^{GFP-} cells. HCMV^{GFP-} cells showed significantly decreased expression of *ifna1*, *ifna2*, and *ifnb*, as well as decreased secretion of IFN-β relative to mock-infected controls. To examine whether IFN-β could initiate differentiation in latently infected cells, we added exogenous IFN-β to the culture. In HCMV^{GFP-} cells, treatment with IFN-β increased the proportion of CD38$^+$ cells relative to untreated controls, indicating induction of myelopoiesis. The myeloid subsets were elevated,

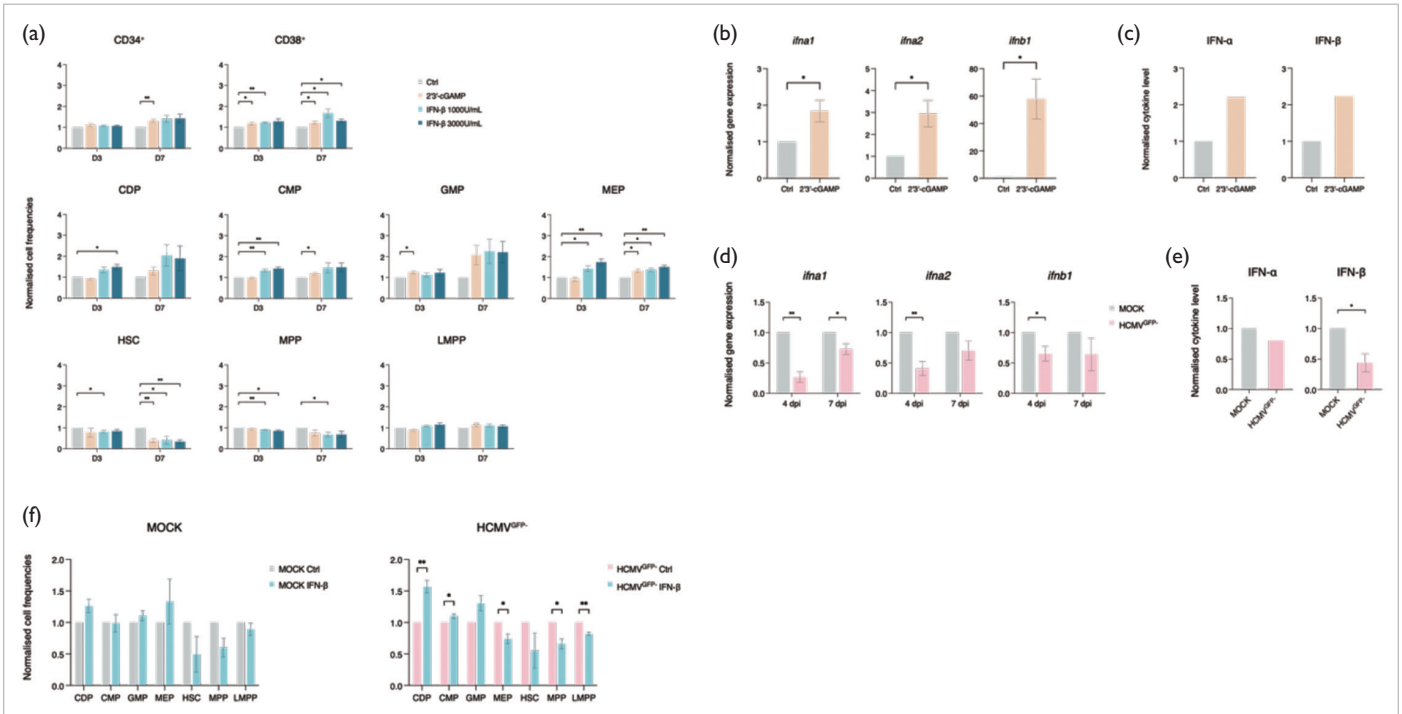

FIG 1. Evaluation of IFN-β-induced myeloid differentiation in CD34$^+$ cells regulated by latent HCMV infection: (a) flow cytometric analysis of CD34$^+$ cell subsets after 2′3′-cGAMP or IFN-β treatment, (b to e) effects of 2′3′-cGAMP or HCMV infection on type-I IFN expression according to qRT-PCR or ELISA, and (f) effect of IFN-β on CD34$^+$ cell differentiation.

Abbreviations: CDP=common dendritic cell progenitor, CMP=common myeloid progenitor, dpi=days post-infection, ELISA=enzyme-linked immunosorbent assay, GMP=granulocyte-macrophage progenitor, HCMV= human cytomegalovirus, HSC=haematopoietic stem cell, IFN-α/β=interferon alpha/beta, LMPP=lymphoid-primed multipotent progenitor, MEP=megakaryocyte-erythroid progenitor, MPP=multipotent progenitor, qRT-PCR= quantitative reverse transcription polymerase chain reaction

whereas the non-myeloid subsets decreased in relative abundance. Similar differentiation patterns were observed in mock-infected cells treated with IFN-β. These results demonstrate that type-I IFNs attribute to myeloid differentiation in CD34+ cells and are likely inhibited by latent HCMV to prevent the development of immune-competent cells.

The STING pathway is activated in CD34+ cells with latent HCMV infection

STING is a key adaptor protein involved in innate immune activation, responding to DNA sensors to recognise viral DNA in HCMV-infected cells. It initiates a type-I IFN response by activating TANK-binding kinase 1 (TBK1), which subsequently drives the phosphorylation of interferon regulatory factor 3 (IRF3). To investigate how latent HCMV suppresses type-I IFN expression, we examined STING pathway activation in CD34+ cells. We also assessed the DNA sensor cGAS, which functions upstream of STING. Unexpectedly, HCMV^{GFP-} cells exhibited elevated expression of *cgas* and *sting1* genes compared with mock-infected controls (Fig 2). This observation was confirmed by Western blot analysis, where protein levels of cGAS and STING, along with downstream signalling molecules TBK1 and IRF3 and their phosphorylated forms, were substantially increased after HCMV latent infection relative to mock-infected controls.

Translocation of p-IRF3 is inhibited by latent HCMV to prevent type-I IFN expression

We next sought to determine whether latent HCMV infection inhibits p-IRF3 nuclear translocation. Confocal microscopy was used to examine mock-infected and HCMV^{GFP-} cells with or without stimulation by 2′3′-cGAMP. In the absence of stimulation, mock-infected cells showed minimal p-IRF3 signal, whereas HCMV^{GFP-} cells displayed elevated cytoplasmic p-IRF3 signal without distinct nuclear localisation. This finding is consistent with the increased p-TBK1 and p-IRF3 levels detected by Western blot analysis. In contrast, HCMV^{GFP+} cells showed elevated p-IRF3 signals in both the cytoplasm and nucleus, indicating active translocation in productively infected CD34+ cells. After 2′3′-cGAMP stimulation, p-IRF3 signal intensity increased across mock, HCMV^{GFP-}, and HCMV^{GFP+} cells. However, nuclear p-IRF3 was observed only in mock and HCMV^{GFP+} cells, not in HCMV^{GFP-} cells, where p-IRF3 was predominantly retained in the cytoplasm. Signal intensity analysis revealed that both HCMV^{GFP-} and HCMV^{GFP+} cells had increased p-IRF3 levels compared with mock-infected controls prior to stimulation. After stimulation, only mock-infected cells exhibited further increases in p-IRF3 intensity. These findings suggest that latent HCMV activates the STING/p-TBK1/p-IRF3 pathway but inhibits p-IRF3 nuclear translocation, thereby reducing type-I IFN expression and preventing CD34+ cell differentiation.

Urine HCMV-DNA presence is correlated with EODs among patients with stage 2/3 HIV-1 infection

Using a Cox regression model, we evaluated correlation between the presence of HCMV DNA and EOD onset. Analysis parameters included

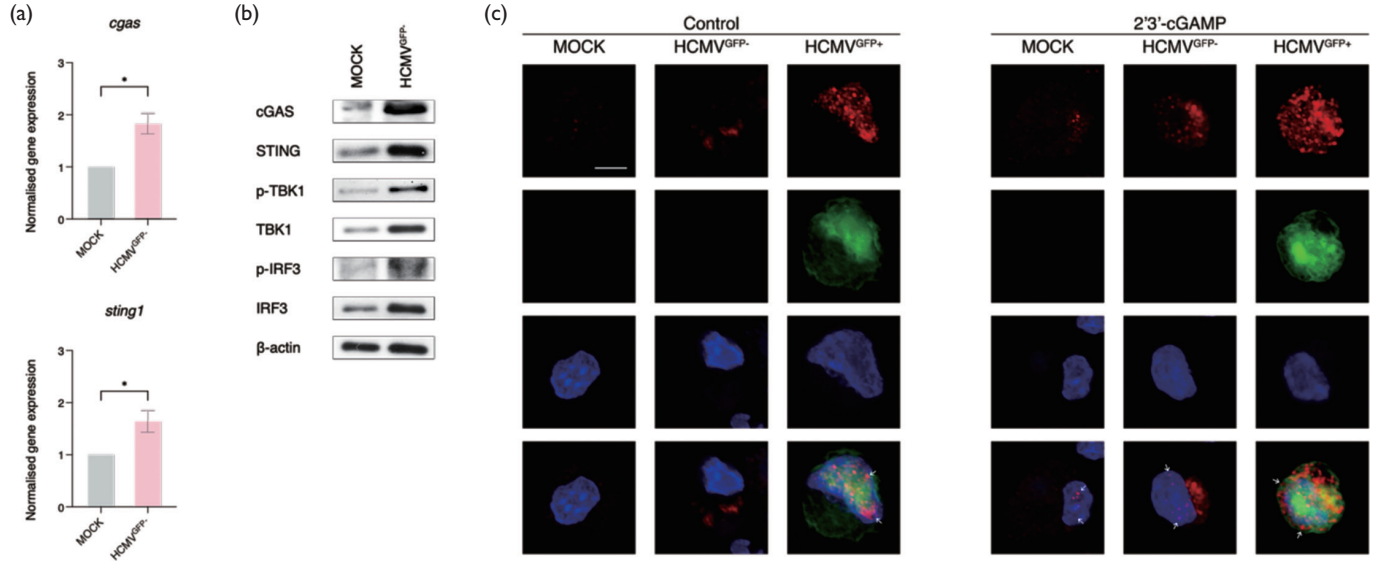

FIG 2. Latent human cytomegalovirus (HCMV) promotes STING pathway activation but prevents p-IRF3 translocation in CD34+ cells: (a) qRT-PCR of *cgas* and *sting1*, (b) Western blot analysis of STING pathway proteins, and (c) confocal microscopy of p-IRF3 signals during HCMV infection (red=p-IRF3, green=HCMV-GFP, blue=DAPI).

HCMV-DNA copy numbers in blood and urine, CD4 counts, HIV-1 RNA copy numbers, and EOD incidence across patient subgroups. In the $HCMV^{blood-}$ subgroup, only one of 26 patients exhibited no EODs; in the $HCMV^{blood+}$ subgroup, only one of 38 patients exhibited no EODs. In the latter group, significance was evident only for skin disease (adjusted hazard ratio [HR]=1.960, 95% confidence interval [CI]=0.922-3.600, P=0.045, Fig 3). In the $HCMV^{urine-}$ and $HCMV^{urine+}$ subgroups, four of 51 and zero of 118 patients, respectively, had no EODs. Significant HRs were observed in the $HCMV^{urine+}$ subgroup for cardiovascular diseases (adjusted HR=0.696, 95% CI=0.492-0.953, P=0.030) and lung diseases (adjusted HR=1.939, 95% CI=1.326-2.761, P<0.001). No significant associations were identified in the $HCMV^{urine-}$ subgroup. Incidence rates of other EOD categories did not differ significantly between groups.

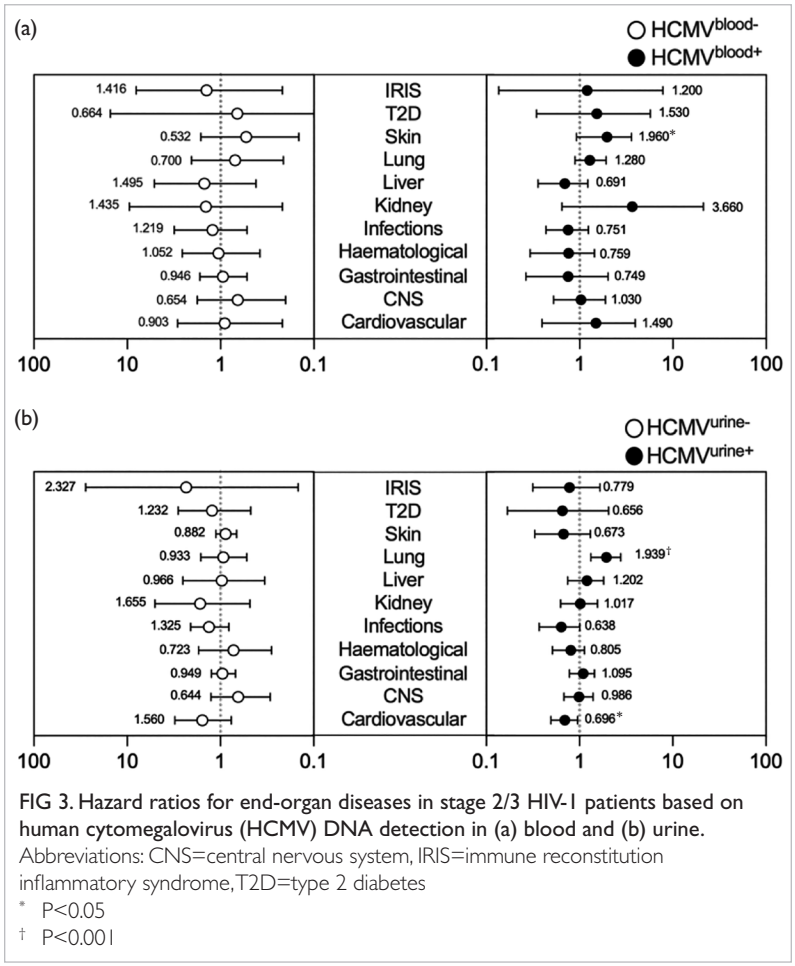

FIG 3. Hazard ratios for end-organ diseases in stage 2/3 HIV-1 patients based on human cytomegalovirus (HCMV) DNA detection in (a) blood and (b) urine.
Abbreviations: CNS=central nervous system, IRIS=immune reconstitution inflammatory syndrome, T2D=type 2 diabetes
* P<0.05
† P<0.001

Discussion

During latency in $CD34^+$ cells, HCMV modulates the STING pathway by inhibiting downstream p-IRF3 nuclear translocation, thus suppressing type-I IFN expression. This suppression prevents $CD34^+$ cells from differentiating into functional antigen-presenting cells, ensuring viral persistence within latent reservoirs. Identification of the HCMV protein responsible for this inhibition is essential for developing therapeutic strategies that restore p-IRF3 activity. The persistence of HCMV as a latent reservoir represents a substantial threat for individuals living with HIV-1, given its association with EODs. Accordingly, we recommend routine testing for HCMV DNA in patients with early-stage HIV-1 infection. For those exhibiting HCMV DNA positivity, treatment with anti-HCMV agents should be considered to delay or manage the onset of EODs, particularly lung and cardiovascular complications.

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Disclosure

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1. Zhao F, Fung TY, Chen Z, Wang H, Cheung AKL. Association of human cytomegalovirus in urine with end-organ diseases in stage 2/3 HIV-1-infected individuals. J Clin Virol 2023;158:105351.

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Effect of Wuzi Yanzong on semen quality in subfertile men: a double-blind, randomised, placebo-controlled trial (abridged secondary publication)

TC Li, RCC Wang, ZX Lin, GWS Kong, JPW Chung, HW Lok, DYL Chan *

KEY MESSAGES

1. In patients with suboptimal semen quality, the traditional Chinese medicine Wuzi Yanzong did not demonstrate a therapeutic effect on semen quality at 3 months.
2. The duration and dosage used in this study may be insufficient to improve semen quality in subfertile men. Nonetheless, the pill appears safe for long-term use.

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Introduction

In developed regions, male infertility accounts for approximately half of all infertility cases. Poor sperm motility and low sperm counts are the most common causes. Wuzi Yanzong (WZYZ) is a traditional Chinese medicine formula widely used to improve semen quality. This study aimed to investigate the therapeutic effect of modified WZYZ on semen quality, sperm function, and natural conception outcomes.

Methods

Men with a total motile sperm count of <20 million were recruited from a university hospital in Hong Kong and randomly assigned to receive either a placebo or WZYZ twice daily for 3 months. Semen samples were collected at baseline, 6 weeks, 3 months, and 6 months to assess semen quality and natural pregnancy outcomes, if any. The total motile sperm count is the most predictive factor for achieving pregnancy. Patients were excluded if infertility was attributed to removal of one testicle, a history of undescended testis, previous chemotherapy, testicular torsion, other known abnormalities of the reproductive organs, azoospermia (indicating structural or chromosomal abnormalities), or known chromosomal disorders. The primary outcome was semen quality. Secondary outcomes included the clinical pregnancy rate, live birth rate, and adverse effects.

WZYZ is composed of *Lycii fructus* (枸杞子) 2.4 g, *Rubi fructus* (覆盆子) 3 g, *Cuscutae Chinensis Semen* (菟絲子) 2.4 g, *Rehmanniae Glutinosae Conquitae Radix* (熟地黃) 3 g, *Polygonati Rhizoma* (黃精) 3 g, *Cistanches Deserticolae Herba* (肉蓯蓉) 2 g, *Epimedii Herba* (仙靈脾) 2 g, *Plantaginis Semen* (車前子) 2 g, and *Cornus Cervi Colla* (鹿角膠) 1.6 g. The total daily dose of 21.4 g was divided into two oral doses.

Results

Of 253 patients recruited, 230 (113 in the control group and 117 in the treatment group) completed the entire treatment course and were assessed at all follow-up visits. The intention-to-treat analysis indicated that WZYZ did not exert any therapeutic effects on sperm motility, sperm concentration, or total motile sperm at any follow-up point. Nonetheless, both groups demonstrated upward trends in sperm concentration, total motile sperm, and motility over the treatment course compared with baseline values. This improvement might be attributable to healthier lifestyle practices adopted after participants became aware of their poor semen quality.

Patients who reported taking supplements showed significant increases in total motility and semen volume; there was a synergistic effect between supplements and WZYZ on sperm concentration. Patients who took supplements exhibited a higher 2-year pregnancy rate. Additionally, there was a synergistic effect between smoking and WZYZ on total motility.

Conclusion

WZYZ demonstrated neither beneficial nor harmful effects on semen parameters or natural conception rates. A standard dosage of WZYZ is not recommended for men with suboptimal semen parameters.

Funding

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Disclosure

The results of this research have been previously published in:

1. Zhao M, Chan CPS, Cheung CWC, et al. A double-blinded, randomized placebo-controlled trial on the effect of traditional Chinese medicine formula Wuzi Yanzong pill on improving semen qualities in men with suboptimal parameters. Trials 2019;20:540.

Barriers and facilitators of implementing post-discharge information summary among healthcare professionals: abridged secondary publication

ELY Wong *, KS Tang, D Dong, PKH Mo, AWL Cheung, EK Yeoh

KEY MESSAGES

1. This study aimed to develop a comprehensive strategy package to enhance implementation of post-discharge information summary (PDIS) for improving patient experience and health-related quality of life.
2. Factors associated with healthcare professionals such as knowledge of PDIS, agreement on roles and responsibilities, attitudes towards the intervention, implementation intentions, and goal setting were emphasised for post-discharge self-management among hospitalised older patients.

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Introduction

Post-discharge information summary (PDIS) can enhance the provision of medicine information to discharged patients or their caregivers. This study aimed to (1) identify barriers and facilitators to the implementation of PDIS by healthcare professionals in public hospitals using the Theoretical Domains Framework (TDF),[1] (2) identify behavioural strategies to address context-specific implementation issues of PDIS using the Behaviour Change Wheel (BCW) and realist evaluation framework, and (3) develop implementation strategies for PDIS through Delphi discussions.

Methods

A mixed-methods design was used to identify hospital stakeholders' perceived barriers and facilitators to the implementation of PDIS in geriatric and general medicine care.

Doctors, nurses, and pharmacists were interviewed to investigate their behavioural and contextual perspectives, as well as their views regarding how to facilitate PDIS, with the goal of identifying barriers and facilitators to implementation of PDIS.

Strategies for implementation were developed using the BCW.[2] Three broad BCW components—capability, opportunity, and motivation (COM-B)—were mapped to identify the target behaviour. The linked COM-B model and TDF were used to establish the behavioural diagnosis, then determine changes needed to enable adoption and enhancement of PDIS. Additionally, specific implementation strategies were examined to address each identified barrier and reinforce each facilitator, in alignment with the red zone of the BCW. An assessment was conducted to determine policies required to support the delivery of these implementation strategies. Behaviour change techniques were applied to select and enact appropriate intervention functions. Realist evaluation was performed to capture the range of causal mechanisms involved in behaviour change.[3]

A final implementation strategy was developed through Delphi discussions involving 12 experts. The strategies were evaluated for relevance, acceptability, and feasibility using a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), within the context of the current discharge process in public hospitals. Two rounds of discussions were conducted, and 15 implementation strategies were generated. A strategy was endorsed if ≥75% of the experts rated it as 4 (agree) or 5 (strongly agree) across all three criteria.[4] Experts were asked to provide comments or suggestions for any strategies that received a rating of ≤3. In the follow-up round, they were asked to re-evaluate strategies that had not reached either a positive or negative consensus on any criterion; they were also asked to assess any newly proposed or modified strategies. A strategy was prioritised if it achieved positive consensus on all three criteria in either round 1 or round 2. Techniques that achieved positive consensus on only two of the evaluation criteria were considered second priority, whereas those that achieved positive consensus on only one criterion were considered third priority.

TABLE 1. Characteristics of participants.

Characteristic	Doctors (n=37)*	Nurses (n=53)*	Pharmacists (n=8)*
Sex			
Male	25 (67.6)	17 (32.1)	1 (12.5)
Female	12 (32.4)	36 (67.9)	7 (87.5)
Age, y			
18-30	6 (16.2)	16 (30.2)	1 (12.5)
31-40	17 (45.9)	28 (52.8)	7 (87.5)
41-50	7 (18.9)	7 (13.2)	0
51-60	7 (18.9)	2 (3.8)	0
Education level			
High school diploma	0	3 (5.7)	0
Bachelor's degree	34 (91.9)	28 (52.8)	0
Master's degree or above	3 (8.1)	22 (41.5)	8 (100.0)
Working experience, y			
0-5	7 (18.9)	12 (22.6)	1 (12.5)
6-10	13 (35.1)	20 (37.7)	4 (50.0)
11-15	3 (8.1)	11 (20.8)	2 (25.0)
16-20	6 (16.2)	3 (5.7)	1 (12.5)
21-25	4 (10.8)	3 (5.7)	0
>25	4 (10.8)	4 (7.5)	0
Rank			
Resident/medical officer	14 (37.8)	-	-
Senior medical office/associate consultant	18 (48.6)	-	-
Consultant	5 (13.5)	-	-
Enrolled/registered nurse	-	31 (58.5)	-
Advanced practice nurse	-	20 (37.7)	-
Ward manager	-	2 (3.8)	-
Pharmacist	-	-	8 (100)
Hospital			
A	8 (21.6)	12 (22.6)	2 (25.0)
B	11 (29.7)	17 (32.1)	2 (25.0)
C	10 (27.0)	12 (22.6)	2 (25.0)
D	8 (21.6)	12 (22.6)	2 (25.0)
Post-discharge information summary			
Heard of			
Yes	35 (94.6)	53 (100)	8 (100)
No	2 (5.4)	0	0
Participated			
Yes	10 (27.0)	53 (100)	8 (100)
No	27 (73.0)	0	0
Received information/training			
Yes	11 (29.7)	38 (71.7)	7 (87.5)
No	26 (70.3)	15 (28.3)	1 (12.5)
Involved in design			
Yes	5 (13.5)	3 (5.7)	3 (37.5)
No	32 (86.5)	50 (94.3)	5 (62.5)

* Data are presented as No. (%) of participants

Results

In total, 98 interviews were conducted with doctors (n=37), nurses (n=53), and pharmacists (n=8). Among the participants, 72.4% (100% of nurses and pharmacists and 27% of doctors) had experience using the PDIS system (Table 1).

Overall, 35 themes and 52 beliefs across 14 TDF domains were identified (Table 2). Of these, 13 TDF domains consisting of 36 belief statements were considered major factors. Key barriers included the content of the information (environmental context and resources), communication among healthcare professionals (social influences), limited knowledge of the objective (knowledge), practice based on individual discretion (behavioural regulation), and negative attitudes towards the value of PDIS (beliefs about consequences). Key facilitators included positive attitudes towards the value of PDIS (beliefs about consequences), agreement on the responsibility for PDIS (social/professional role and identity), diffusion of PDIS (environmental context and resources), features of PDIS (environmental context and resources), confidence in implementation (beliefs about capability), knowledge of responsibilities (knowledge), and goal setting (goals).

The major TDF domains were categorised into the COM-B components. The APEASE criteria (affordability, practicability, effectiveness and cost-effectiveness, acceptability, side effects/safety, and equity) were utilised to assess relevance. Four policy categories were selected to support the four intervention functions: communication/marketing, guideline development, environmental/social planning, and service provision.

Possible behaviour change techniques were examined. The 11 most frequently used techniques were selected based on the APEASE criteria: providing information about social and environmental consequences, providing information about health consequences, offering feedback on behavioural outcomes, using credible sources, demonstrating the behaviour, introducing how to perform the behaviour, offering practical social support, restructuring the physical environment, restructuring the social environment, problem solving, and action planning.

A realist evaluation was conducted for each strategy to uncover the underlying mechanisms and contextual factors. The intended outcomes included improved acceptability, adoption, uptake, fidelity, and sustainability.

Two male and 10 female experts in PDIS (including three consultants, two ward managers, two department operation managers, two pharmacy managers, two pharmacists, and one quality and safety manager) participated in the Delphi survey (Table 3).

TABLE 2. Theoretical domains framework (TDF) domains, belief statements, and illustrative quotes for post-discharge information summary (PDIS).

TDF domain and theme	Belief statement	No. of participants (n=98)	Illustrative quote
Knowledge			
Awareness	I am not aware of PDIS	6	"Actually, many doctors are not aware of this (PDIS)." (D09)
Knowledge	I have/lack knowledge regarding the PDIS objective (development path, purpose, and goal)*	72	"I am clear and understand the background and objective of this programme." (N18) "I am clear about why the database only lists common side effects." (D69)
	I have/lack knowledge regarding the PDIS content (what information is on the PDIS, where to print, when to distribute, whom to serve)*	33	"I will only distribute the PDIS form to patients discharged to home, not including patients discharged to elderly homes or transferred to other hospitals." (N31)
	I have/lack knowledge regarding my role responsibility for PDIS*	33	"Nurses are responsible for distributing this form and explaining to patients about their medication and follow-ups." (N04)
Skills			
Practising	I need constant practice to implement PDIS*	16	"I need to practice to get familiar with this new platform." (N28)
Training	Training helps with the implementation of PDIS/training is not necessary; ward manager is enough*	13	"No formal training for newcomers. They just informed me that I should practice PDIS." (N50)
Competency	I can/cannot handle this task with my professional knowledge*	12	"I have not encountered any difficulties when instructing PDIS because of my professional knowledge and ample work experience." (N05)
Social/professional role and identity			
Agreement on role responsibility	I agree/do not agree with my role responsibility for PDIS*	70	"The instruction work done by nurses is really the best choice. The discharge guidance is all done by the nurse. It is also good to take PDIS as a reference." (N86)
Representative	A PDIS representative is a key person in implementation*	16	"We have a PDIS representative who is responsible for collecting front-line staff's feedback and participating in related meetings." (P76)
Role seniority	Professional seniority impacts the implementation of PDIS	3	"Junior staff may be afraid of explaining medication side effects to patients or caregivers." (N35)
Beliefs about capability			
Confidence in implementation	I am/am not confident that I am able to print out the PDIS*	43	"In fact, it is easy to print it out and does not take much time. It is a convenient process." (N04)
	I am/am not confident that I am able to instruct patients about medication side effects listed on the PDIS*	27	"I think the side effects listed on PDIS are all very common drugs, so for the time being I think we can handle them." (N84)
Optimism			
Optimism	I am optimistic about the future development of PDIS	5	"I believe PDIS can be sustained over the long term." (N03)
Beliefs about consequences			
Attitude towards the value of PDIS	I think PDIS is/is not useful to patients/caregivers*	86	"The patients in Hong Kong, especially the elderly, may not pay attention to what medicines they are taking, such as whether a medicine is old or new, and what the side effects are. If you remind them, they are usually very grateful." (N20)
	I think PDIS is/is not useful to my work*	67	"For the staff, I think PDIS is very helpful because nurses can do medication reconciliation with PDIS. Usually, the nurses will take this form (PDIS) to go through all the details (medication and follow-ups) with patients before discharge, and this reduces the chance of mistakes." (D14)
Reinforcement			
Two-way feedback	I can/cannot give feedback on my practice of PDIS*	19	"We don't have a mechanism to give our feedback on PDIS implementation." (D74)
	I do/do not receive feedback on outcomes from patients/caregivers*	10	"We really want to know the outcome from the patient side, such as whether this form is effective for them." (D19)
Reinforcement	There is a constant reminder about PDIS implementation	4	"The leaders keep reminding us to deliver PDIS over these 2 years." (N03)

* Major belief statements for implementation strategy mapping

TABLE 2. (cont'd)

TDF domain and theme	Belief statement	No. of participants (n=98)	Illustrative quote
Intentions			
Implementation intentions	I am/am not willing to instruct patients/caregivers on the side effects*	51	"We are willing to print this form out because we think it is useful for us." (N15)
	I am willing to print this form for patients/caregivers*	10	"The daily practice is that I will go through all the side effects and read them to patients." (N13)
Goals			
Goal-setting	Distributing PDIS to every discharged case is mandatory/voluntary*	53	"PDIS is mandatory in our department." (N02)
Memory, attention, and decision processes			
Memory	PDIS is my routine practice/I usually forget PDIS during patient discharge*	38	"PDIS is routine practice right now. We take it as the starting point to communicate with patients." (N25)
Decision making	PDIS is/is not a priority when performing discharge education with multiple materials on hand*	33	"The discharge summary is an important document that must be printed out because patients will encounter problems without it. On the contrary, PDIS may not have a great impact on patients—we sometimes forget to print it out." (N28)
	I implement PDIS based on own discretion*	43	"Under certain circumstances, I probably won't print PDIS for them, for example, when patients already receive too many written discharge documents, I am afraid it would be overwhelming." (N02)
Cognitive overload	There are many other similar initiatives in my department	2	"When introducing PDIS, nurses might feel fatigued by these changes." (N36)
Environmental context and resources			
Information flow	Information circulation about PDIS is/is not sufficient and smooth between the committee/working group and front-line staff*	76	"No one introduced PDIS to me; I found it myself." (D16) "There is no updated information after the first introduction meeting." (D23) "No information about the PDIS development background or goals, only practical information such as how to print the forms." (N18)
Characteristics	Information on PDIS is/is not clear to patients/caregivers*	54	"I think the wording is appropriate. Patients won't find it difficult to understand." (N04)
	The PDIS drug database coverage is insufficient*	36	"Some new drugs that are important for patients to understand in terms of side effects are not covered by the current database." (N07)
	The Chinese version is sufficient/insufficient for the current patient population*	28	"The Chinese version is sufficient for our current patient population. There are very few foreigners in our cluster." (N29) "PDIS is not useful for patients who cannot understand Chinese. We usually have foreign patients, such as domestic workers." (D23)
	Current side effect information is sufficient/insufficient/excessive for educating patients/caregivers*	23	"I think the current side effect information is sufficient. Too much detail would make it complicated for patients." (N12)
	Information coverage in PDIS is sufficient/insufficient/excessive for me to educate patients/caregivers*	18	"If PDIS could list changes in medication, it would be more helpful for patients." (P47) "It would be better if PDIS included medication-taking instructions. For example, for diabetes medicine, we usually tell patients to take it with meals, but not if they have no appetite." (N30)
	The PDIS platform design is/is not user-friendly*	18	"The PDIS platform is easy to use. I just need to click several times to print it out." (N86)
Patient characteristics	PDIS is not suitable for the elderly population	9	"I am afraid elderly patients cannot scan the QR code to learn more about their medication due to low e-health literacy." (N06)
Resources	There are time constraints when handling PDIS*	26	"Usually, patients are rushed during discharge from the hospital. We have little time to give detailed explanations." (N06) "I need to discharge several patients at once, so I can spend limited time on each patient." (N07) "Usually, a patient has a lot of medications, which makes it difficult to go through all of them during the discharge period." (N18) "Sometimes we forget to print PDIS because we are too busy." (N78)
	There are not enough staff or facilities to handle the practice of PDIS	6	"We have high staff turnover because of COVID-19. We don't have enough time to give detailed explanations." (N25)

TABLE 2. (cont'd)

TDF domain and theme	Belief statement	No. of participants (n=98)	Illustrative quote
COVID-19	COVID-19 impacts the implementation of PDIS*	11	"We have high staff turnover because of COVID-19. We don't have enough time to give detailed explanations." (N25)
Organisational culture	I implement PDIS because of a top-down organisational culture in my department	7	"Because we have a top-down culture, we just follow what the leaders instruct us to do." (D21)
Social influences			
Communication among staff	I seldom/usually share experiences of using PDIS with my colleagues*	58	"Some colleagues shared their experiences with PDIS practices so that we could implement it (PDIS) in a better way." (N13)
Cooperation among staff	I can/cannot get support from my colleagues in practising PDIS*	37	"Clerks will help check whether PDIS is printed and remind us if not." (N13)
Patient-provider interaction	My interaction with patients positively/negatively impacts my practice of PDIS*	39	"I was worried about the negative impact of PDIS on patients, but so far I have never heard anything back from them. So I realised the concern was unnecessary." (D10)
Leadership support	I can/cannot get support from my leaders*	22	"At first, many colleagues forgot to distribute the PDIS form; therefore, our manager created a stamp and placed it on the PDIS form to remind clerks to distribute it to patients." (N58)
Conformity	I perceive the value of PDIS in this way because it reflects the shared beliefs in my ward*	13	"We all think PDIS is beneficial for our work." (N04)
	I practice PDIS in this way because it is the common practice in my ward	7	"Our common practice is holding the discharge summary to carry out discharge education." (N33)
Emotion			
Feelings	I feel/do not feel anxious when instructing patients about side effects*	53	"I am not worried about letting patients see the side effects information, and I think this form actually helps me educate patients by serving as a reference." (N52) "I am worried that patients won't take their medications if they see those side effects, and they will ask many questions about those side effects." (N28)
Behavioural regulation			
Action planning	I have/do not have an action plan when encountering potential problems*	39	"I will add necessary information into PDIS if patients ask why some drugs do not have side effects listed." (N02)
Audit	There is/is not an evaluation mechanism in my department	9	"We never evaluate compliance with PDIS implementation." (D01)
	I have a checklist to support self-monitoring*	11	"We have a discharge checklist to ensure we distribute PDIS to patients." (N03)
Feedback	I can/cannot receive programme outcome feedback*	10	"We really want to know the outcome from the patient side, such as whether this form is effective for them." (D19)
Implementation protocol	There is/is not a protocol for implementing PDIS	8	"It's important to have a standardised operation to teach staff how to execute PDIS." (D09)

In round 1, 10 (66.7%) strategy items reached consensus on relevance, acceptability, and feasibility. Three strategy items were deemed relevant and acceptable but did not reach consensus on feasibility. One item required improvement in acceptability, and one item did not achieve agreement on both acceptability and feasibility. Therefore, these five strategy items were revised and included in round 2 of voting. In round 2, all five revised strategy items achieved consensus on relevance, acceptability, and feasibility. The final implementation strategy package was endorsed and included 15 items across five categories: environmental restructuring, feedback, training, communication, and guideline development.

Discussion

The BCW framework proved valuable in transitioning from exploratory research on PDIS implementation to the formulation of an implementation intervention, particularly concerning healthcare professionals. The behaviour change techniques facilitated identification of specific intervention content, using standardised labels and definitions. The standardised terminology

TABLE 3. Proposed implementation strategy items for post-discharge information summary (PDIS) based on Delphi survey

Implementation strategy item		% of experts in agreement (n=12)			
		Relevance	Acceptability	Feasibility	Consensus
1. Refine the PDIS form: review the current discharge drug list in the medical department and update the PDIS drug coverage (expanding from 80% to 90%)	Round 1	100	83.0	83.0	Yes
	Round 2	-	-	-	-
2. Create an English version of the PDIS form to accommodate a wider range of ethnicities	Round 1	100	92.0	92.0	Yes
	Round 2	-	-	-	-
3. Establish a two-way platform between nursing staff and the PDIS committee to enhance the information flow related to PDIS	Round 1	92.0	92.0	75.0	Yes
	Round 2	-	-	-	-
4. Establish a referral platform to direct inquiries to pharmacists at the dispensary to help explaining side effects After revision: Establish a referral platform with a separate queue for PDIS inquiries supported by manpower and information technology infrastructure	Round 1	92.0	83.0	58.0	No
	Round 2	92.0	100	75.0	Yes
5. Invite patients to provide positive feedback to foster positive beliefs regarding the consequences of PDIS	Round 1	100	92.0	92.0	Yes
	Round 2	-	-	-	-
6. Invite peers to share positive experiences with PDIS to encourage positive beliefs about its implementation	Round 1	83.0	83.0	83.0	Yes
	Round 2	-	-	-	-
7. Provide feedback on positive outcomes for both nurses and patients to educate and persuade staff, thereby strengthening positive beliefs about PDIS	Round 1	100	100	83.0	Yes
	Round 2	-	-	-	-
8. Incorporate medication side effects and warning signals into the discharge slip After revision: Incorporate medication side effects and warning signals into Hospital Authority Go, providing options for both electronic and printed copies	Round 1	83.0	83.0	58.0	No
	Round 2	100	100	100	Yes
9. Incorporate PDIS-related knowledge and skills training into the regular training for newcomers, demonstrating how to explain medication side effects and use PDIS in the Clinical Management System	Round 1	92.0	92.0	83.0	Yes
	Round 2	-	-	-	-
10. Set up a sharing platform (eg, forum or newsletter) to encourage nurses to exchange views and experiences regarding PDIS-related behaviours and techniques After revision: Use newsletters (personal interview format) to encourage nurses to share their views and experiences related to PDIS implementation	Round 1	83.0	67.0	75.0	No
	Round 2	83.0	75.0	83.0	Yes
11. Establish a training system to update PDIS-related medication knowledge whenever the drug list changes, and to build other necessary skills such as interpersonal communication, to support nurses in delivering PDIS	Round 1	83.0	75.0	83.0	Yes
	Round 2	-	-	-	-
12. Design brochures and produce videos to introduce the background and objectives of PDIS development	Round 1	83.0	83.0	92.0	Yes
	Round 2	-	-	-	-
13. Define job responsibilities and service target populations (eg, distributing the PDIS form and explaining medication side effects and warning signals to each discharged patient or caregiver in the medical ward) by developing formal PDIS implementation guidelines After revision: Define job responsibilities and service target populations (eg, distributing and explaining the PDIS to each discharged patient or caregiver) and assign a designated PDIS link person to enhance nurses' knowledge of PDIS	Round 1	75.0	67.0	67.0	No
	Round 2	100	100	100	Yes
14. Establish a hospital-wide review panel to evaluate PDIS implementation regularly and formulate detailed action plans to resolve practical issues (eg, where to find help and who can help when nurses cannot handle side effects explanation, or stepwise solutions when having information technology difficulties), and incorporate these into PDIS implementation guidelines. After Revision: Conduct a Hospital Authority–wide review exercise to regularly evaluate PDIS implementation and formulate practical action plans for problem-solving (eg, where to find help and who can help when nurses cannot handle side effects explanation, or stepwise solutions when information technology difficulties occur), with integration into PDIS implementation guidelines	Round 1	83.0	75.0	67.0	No
	Round 2	83.0	92.0	83.0	Yes
15. Identify opinion leaders (eg, general manager of nursing) and establish a mechanism to communicate the positive impact of PDIS and the importance of nurses' roles, thus promoting positive emotions and agreement with their responsibilities	Round 1	100	83.0	92.0	Yes
	Round 2	-	-	-	-

and predefined stages of the development process facilitated structured discussions within the research team. Five intervention functions were included: education, persuasion, training, enablement, and environmental restructuring, along with four policy categories: communication/marketing, guidelines, environmental/social planning, and service provision. These were used to design a multifaceted

strategy package comprising environmental redesign, feedback provision, multilevel training, communication enhancement, and guideline development. Notably, strategies requiring additional manpower or increased workloads were deemed unacceptable or unfeasible, according to experts' feedback. Strategies involving education, as well as audit and feedback mechanisms, were considered effective in improving professional performance. Future studies are needed to evaluate the effectiveness of implementation strategies by assessing implementation fidelity, self-reported patient-centred outcomes, and clinical outcomes.

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1. Wong ELY, Tang KS, Dong D, et al. Evaluation of the implementation of information system for postdischarge with the theoretical domains framework by healthcare professionals: a multistage design with qualitative inquiry and Delphi expert discussion protocol. BMJ Open 2021;11:e046081.
2. Wang DY, Wong EL, Cheung AW, Tam ZP, Tang KS, Yeoh EK. Implementing the information system for older adult patients post-discharge self-management: a qualitative study. Age Ageing 2024;53:afae136.
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4. Wang DY, Wong ELY, Cheung AWL, Tam ZPY, Tang KS, Yeoh EK. Barriers and facilitators to implementing a nurse-led information system for older adult patients' post-discharge self-care: an exploratory sequential mixed-methods study. J Adv Nurs 2025;0:1-17.
5. Wang DY, Wong EL, Cheung AW, Tam ZP, Tang KS, Yeoh EK. Enhancing implementation of information and communication technologies for post-discharge care among hospitalised older adult patients: development of a multifaceted implementation intervention package using the behavior change wheel and implementation research logic model. Implement Sci Commun 2025;6:52.

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