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Original article

Development and validation of the Chinese osteoporosis screening algorithm (COSA) in identification of people with high risk of osteoporosis

Ching-Lung Cheung [a, b, *], Gloria HY. Li [c], Hang-Long Li [d], Constance Mak [a], Kathryn CB. Tan [d], Annie WC. Kung [d]

[a] Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
[b] Laboratory of Data Discovery for Health (D24H), Hong Kong Science and Technology Park, Hong Kong SAR, China
[c] Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Hong Kong
[d] Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong

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ABSTRACT

Objectives: To enhance the public awareness and facilitate diagnosis of osteoporosis, we aim to develop a new Chinese Osteoporosis Screening Algorithm (COSA) to identify people at high risk of osteoporosis.
Methods: A total of 4747 postmenopausal women and men aged ≥ 50 from the Hong Kong Osteoporosis Study were randomly split into a development (N = 2373) and an internal validation cohort (N = 2374). An external validation cohort comprising 1876 community-dwelling subjects was used to evaluate the positive predictive value (PPV).
Results: Among 11 predictors included, age, sex, weight, and history of fracture were significantly associated with osteoporosis after correction for multiple testing. Age- and sex-stratified models were developed due to the presence of significant sex and age interactions. The area under the curve of the COSA in the internal validation cohort was 0.761 (95% CI, 0.711–0.811), 0.822 (95% CI, 0.792–0.851), and 0.946 (95% CI, 0.908–0.984) for women aged < 65, women aged ≥ 65, and men, respectively. The COSA demonstrated improved reclassification performance when compared to Osteoporosis Self-Assessment Tool for Asians. In the external validation cohort, the PPV of COSA was 40.6%, 59.4%, and 19.4% for women aged < 65, women aged ≥ 65, and men, respectively. In addition, COSA > 0 was associated with an increased 10-year risk of hip fracture in women ≥ 65 (OR, 4.65; 95% CI, 2.24–9.65) and men (OR, 11.51; 95% CI, 4.16–31.81).
Conclusions: We have developed and validated a new osteoporosis screening algorithm, COSA, specific for Hong Kong Chinese.

1. Introduction

Osteoporosis is a prevalent disease affecting hundred millions of people worldwide. We recently projected the hip fracture number in Asia and found that the number of hip fracture will be doubled by 2050 [1]. Thus, there is an urgent need to reduce the incidence of hip fracture, particularly in Asia.

Although osteoporosis is a public health issue, it is widely recognized as an underdiagnosed disease partly due to the limited availability of dual-energy X-ray absorptiometry (DXA), which is the gold standard of bone mineral density (BMD) measurement. For example, the minimum number of DXA machine required for adequate osteoporosis care was established to be 11 per million people [2]. However, many parts of the world have insufficient DXA machines [3]. In particular, people living in the rural areas have restricted access to DXA. Thus, to facilitate early diagnosis of osteoporosis, it is important to develop a simple tool that can help prioritizing people to have DXA scan.

Risk prediction tool is important in guiding clinical management. Previously, Osteoporosis Self-Assessment Tool for Asians (OSTA) was developed by a group of experts to identify Asian

* Corresponding author. Department of Pharmacology and Pharmacy, The University of Hong Kong, Pokfulam, Hong Kong.
E-mail address: lung1212@hku.hk (C.-L. Cheung).
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women who are at high-risk of osteoporosis, using just age and weight as the predictor variables [4]. OSTA was subsequently validated in men [5]. However, the OSTA was developed based on women from different Asian countries and regions. It is now widely recognized that population-specific risk factors are important in developing risk prediction tools. Most importantly, the estimates of the risk factors used in the prediction model must be derived from the population that the model applies. In this study, we aim to develop a new Chinese Osteoporosis Screening Algorithm (COSA) and compare its performance with the OSTA.

2. Methods

2.1. Development and internal validation cohort

In this study, we used the data from the Hong Kong Osteoporosis Study (HKOS) for the development and internal validation. Details of the HKOS has been previous described [6]. In this study, 6120 post-menopausal women and men aged 50 years or above were included. After excluding participants with missing data on femoral neck BMD and/or other predictors (N = 1373), 4747 participants were included in the final analysis. These participants were randomly split into a development (N = 2373) and an internal validation cohort (N = 2374).

2.2. External validation cohort

We recruited and screened 2012 community dwelling participants aged 50 years or above using the COSA questionnaire during 2019–2021 in Kwai Tsing District in Hong Kong. We further invited the high-risk participants identified using the optimal cutoff point of COSA, for DXA scanning.

2.3. Ethics

The ethical approval of this study has been granted by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref: UW03-140 and UW 20–333).

2.4. Variables included in the prediction model development

We selected the risk factors included in the FRAX (age, sex, height, weight, history of fracture, smoking, drinking, use of steroid, and rheumatoid arthritis) except parental history of fracture and secondary osteoporosis. Since parental history of fracture was only available in less than half of the participants, including this variable in the model would largely reduce the sample size. While secondary osteoporosis is a broad term, we included in the model 2 disease predictors (diabetes and stroke) that are closely related to fracture instead. Diabetes is a well-established risk factor of fracture [7], and our recent hip fracture prediction score [8] showed that stroke was a significant predictor of hip fracture in Hong Kong Chinese.

2.5. OSTA

In the validation cohort, we compared the performance of COSA with OSTA in identification of people with osteoporosis. OSTA index was calculated using the following formula: OSTA = 0.2 * [weight (kg) - age (years)]. OSTA < −1 indicated intermediate and high risk of osteoporosis [4].

2.6. Clinical outcomes

Osteoporosis was defined as BMD T-score ≤ −2.5 at the femoral neck. BMD was measured using DXA (Hologic QDR 4500 plus, Waltham, MA, USA). Since BMD at the femoral neck is the most robust predictor of hip fracture, osteoporosis at the femoral neck is used as the primary outcome in the COSA development. The secondary outcome was osteoporosis at either spine or hip (lumbar spine, femoral neck, or total hip). In the association analysis with 10-year risk of incident hip fracture, all participants in the development and validation cohorts were followed for 10 years. Hip fracture status was retrieved from the Clinical Data Analysis and Reporting System (CDARS) and defined using the ICD-9 code of 820.XX [9]. Our previous study showed that the positive predictive value (PPV) of the ICD-9 code is 100% [9]. In this analysis of incident hip fracture, patients who had prevalent hip fracture were excluded. To avoid the possibility of delayed coding in the medical records, hip fracture occurred within 30 days from the baseline visit date were also considered prevalent hip fracture and hence excluded.

2.7. Statistical analysis

The COSA was developed using logistic regression, with bias-corrected accelerated 95% confidence interval (CI) and P-value estimated using 1000 bootstrap resamples. Variables showing significant association with osteoporosis after correction for multiple testing (0.05/11 = 0.0046) were selected to build the COSA model. We evaluated the model interaction with age and sex and found significant interaction, therefore we eventually developed the COSA by obtaining the estimates of the variables in three groups separately: (1) women aged < 65 years; (2) women aged ≥ 65 years; and (3) men. Men were not further divided by age because the limited sample size. The area under the receiver operating characteristic curve (AUC) of the COSA and OSTA were determined. To compare the improvement in classification of osteoporosis of COSA with reference to OSTA, category-less net reclassification index (NRI) and integrated discrimination improvement (IDI) were evaluated using the R package “Hmisc”.

The Youden's index was used to select the cutoff point of the COSA to identify people at high risk of osteoporosis. The final COSA equations were developed by scaling of the beta-coefficient of each variable and the incorporation of the Youden's index, such that an individual with COSA > 0 is at high-risk of osteoporosis. The sensitivity, specificity, PPV, and negative predictive value (NPV) of the Youden's index were calculated. To evaluate if COSA > 0 can predict the 10-year risk of hip fracture, logistic regression was used. Odds ratio (OR) and the corresponding 95% confident interval were reported. Association with P-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS version 22.0 software (IBM, Inc., Chicago, IL, USA) and R (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/).

3. Results

3.1. Development of COSA

Table 1 shows the characteristics of the study participants included in the development and internal validation cohort. The characteristics were similar between the development and internal validation cohorts, except that the development cohort had a high prevalence of rheumatoid arthritis.

Table 2 shows the result of the association of the risk factors with osteoporosis. In the multivariable logistic regression analysis, sex, age, weight, and history of fracture were significantly

Table 1
Demographic characteristics of the HKOS study participants.

	Development cohort		Internal validation cohort		
	Mean or N	SD or %	Mean or N	SD or %	P-value
Age, yr	65.70	9.50	65.80	9.40	0.706
Height, m	1.56	0.09	1.56	0.09	0.267
Weight, kg	57.32	10.55	57.06	10.42	0.395
Female	1573	66.3	1595	67.2	0.511
Ever smoking	396	16.7	355	15.0	0.102
Ever drinking	308	13.0	270	11.4	0.092
History of fracture	579	24.4	594	25.0	0.62
Diabetes	308	13.0	276	11.6	0.156
Stroke	49	2.1	47	2.0	0.835
Use of oral steroids	37	1.6	24	1.0	0.096
Rheumatoid arthritis	16	0.7	5	0.2	0.023
BMD at the femoral neck, g/cm2	0.634	0.129	0.630	0.129	0.325
BMD T-score at the femoral neck	−1.47	1.15	−1.50	1.14	0.302
Osteoporosis at the femoral neck	451	19.0	457	19.3	0.83

Continuous variables are presented as mean and standard deviation (SD). Categorical variables are presented as number (N) and %.

Table 2
Multivariable logistic regression in the development and internal validation cohorts.

Variables used in the model development	Development cohort				Internal validation cohort			
	OR	95% CI		P-value	OR	95% CI		P-value
		lower	Upper			lower	Upper	
Age, yr	1.128	1.106	1.154	0.001	1.116	1.097	1.139	0.001
Height, m	0.195	0.012	3.144	0.234				
Weight, kg	0.901	0.880	0.919	0.001	0.879	0.857	0.896	0.001
Female	15.662	8.681	35.200	0.001	12.787	7.486	26.364	0.001
Ever smoking	1.448	0.791	2.488	0.195				
Ever drinking	0.919	0.456	1.738	0.804				
History of fracture	2.510	1.827	3.512	0.001	2.809	2.075	3.838	0.001
Diabetes	0.770	0.513	1.188	0.212				
Stroke	0.987	0.283	3.292	0.986				
Use of oral steroids	0.951	0.237	2.944	0.924				
Rheumatoid arthritis	6.021	1.155	26.053	0.009				

95% CI and P-values were computed based on 1000 bootstrap samples.

associated with osteoporosis after correction for multiple testing. Similar significant associations of these factors with osteoporosis were also observed in the internal validation cohort (Table 2). Therefore, these variables were used for the risk score development. In the risk score developed based on the beta-estimate of these variables, we found that there was a significant sex and age interaction with the risk score ($P_{interaction} < 0.05$), therefore we developed the risk score in three groups separately, namely women aged < 65 years, women aged ≥ 65 years, and men.

After deriving the COSA score and identifying the Youden's index in each group, the beta coefficient of each variable was scaled and Youden's index was incorporated into the COSA equation, so that COSA score >0 indicates a high risk of osteoporosis. The final equation of the COSA in the 3 groups are provided in Table 3. The AUC of the COSA in the development cohort was 0.810 (95% CI, 0.762–0.859), 0.807 (95% CI, 0.776–0.838), and 0.923 (95% CI, 0.860–0.985) for women aged < 65 years, women aged ≥ 65 years, and men, respectively (Supplementary Table 1 and Supplementary Fig. 1). For osteoporosis at either spine or hip, the AUC of the COSA are provided in Supplementary Table 1.

3.2. Internal validation of COSA

In the internal validation cohort, we compared the performance of COSA with reference to OSTA in risk stratification of osteoporosis (Table 4). In all the 3 groups, the COSA had higher AUC (Supplementary Fig. 2) and accuracy than OSTA in the identification of subjects with high risk of osteoporosis at the femoral neck (Table 4). Using IDI and category-less NRI, COSA had a significant improvement in the reclassification of osteoporosis compared to

Table 3
The original and scaled beta-coefficient for COSA.

	Women aged <65 years		Women aged ≥65 years		Men	
	Beta	Scaled beta	Beta	Scaled beta	Beta	Scaled beta
Age, yr	0.105	3	0.099	2	0.077	1
Weight, kg	−0.143	−4	−0.092	−2	−0.151	−2
History of fracture	1.057	32	0.814	17	1.308	17
Constant	−1.237	17[a]	−2.771	−53[a]	−1.036	34[a]
Equation	17 + (age *3) + (weight * −4) + (history of fracture * 32)		−53 + (age * 2) + (weight * −2) + (history of fracture * 17)		34 + (age* 1) + (weight * −2) + (history of fracture * 17)	

[a] The scaled beta of the constant included the Youden's index, such that the COSA score > 0 indicates a high risk of osteoporosis.

Table 4
The risk stratification of COSA and OSTA in the internal validation cohort in (a) women aged<65 years, (b) women aged ≥65 years, and (c) men.

(a) Women aged <65 years				
	COSA		OSTA	
	Value	95% CI	Value	95% CI
AUC	0.761	0.711 to 0.811	0.736	0.685 to 0.787
Sensitivity	57.47%	46.41%–68.01%	67.82%	56.94%–77.44%
Specificity	78.16%	75.05%–81.05%	63.55%	60.02%–66.98%
PPV	23.15%	19.38%–27.40%	17.56%	15.20%–20.20%
NPV	94.14%	92.61%–95.36%	94.52%	92.68%–95.92%
Accuracy	76.03%	73.01%–78.87%	63.99%	60.65%–67.23%
(b) Women aged ≥65 years				
	COSA		OSTA	
	Value	95% CI	Value	95% CI
AUC	0.822	0.792 to 0.851	0.814	0.783 to 0.844
Sensitivity	67.16%	61.87%–72.14%	97.34%	95.01%–98.78%
Specificity	80.00%	75.80%–83.77%	18.05%	14.45%–22.12%
PPV	73.46%	69.23%–77.31%	49.47%	48.26%–50.69%
NPV	74.72%	71.58%–77.62%	89.16%	80.69%–94.18%
Accuracy	74.20%	70.90%–77.30%	53.88%	50.23%–57.49%
(c) Men				
	COSA		OSTA	
	Value	95% CI	Value	95% CI
AUC	0.946	0.908 to 0.984	0.930	0.884 to 0.976
Sensitivity	90.62%	74.98%–98.02%	96.88%	83.78%–99.92%
Specificity	86.08%	83.39%–88.48%	53.28%	49.63%–56.91%
PPV	21.80%	18.43%–25.60%	8.16%	7.45%–8.93%
NPV	99.54%	98.65%–99.84%	99.75%	98.30%–99.96%
Accuracy	86.26%	83.65%–88.60%	55.07%	51.50%–58.60%

AUC was evaluated using continuous COSA and OSTA, while the other parameters were evaluated using the optimal cutoff (COSA >0 and OSTA ≤ −1). AUC: area under the receiver operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value.

OSTA in all the 3 groups (Table 5; all P < 0.05). Similar significant improvement was observed in reclassification of osteoporosis at either spine or hip (data not shown).

3.3. External validation of COSA

The PPV of the COSA was assessed in the external validation cohort comprising community-dwelling subjects. We screened 1876 community dwelling participants (1484 women and 392 men) without missing data (Supplementary Table 2). Among the 1876 participants, 359 women and 60 men had the COSA >0 and were invited to have a DXA scan. A total of 116 women (32.3%) and 29 men (48.3%) declined to have a DXA scan, leaving 243 women and 31 men in the final analyses.

The DXA result of the subjects with COSA > 0 is shown in Supplementary Table 3. Among the 133 women aged < 65, 54 (40.6%), 70 (52.6%), and 9 (6.8%) had osteoporosis, osteopenia, and normal BMD, respectively, resulting in a PPV of 40.6%. Among the 143 women aged ≥ 65, 85 (59.4%), 51 (35.7%) and 7 (4.9%) had osteoporosis, osteopenia, and normal BMD, respectively, resulting a PPV of 59.4%. Among the 31 men, 6 (19.4%), 17 (54.8%), and 8 (25.8%) had osteoporosis, osteopenia, and normal BMD, respectively, resulting a PPV of 19.4%.

3.4. Association of COSA with 10-year risk of incident hip fracture

In the development cohort, participants with COSA > 0 was significantly associated with a higher 10-year risk of hip fracture with an OR of 4.80 (95% CI, 2.43–9.48; P < 0.001) and 3.79 (95% CI, 1.22–11.79; P = 0.022) in women aged ≥ 65 and men, respectively. No significant association with hip fracture was observed in women aged < 65 (OR, 3.54 [95% CI, 0.71–17.68]; P = 0.124; Table 6). Similar associations were observed in the validation cohort with an OR, 4.96 (95% CI, 0.51–47.91; P = 0.166), 4.65 (95% CI, 2.24–9.65; P < 0.001) and 11.51 (95% CI, 4.16–31.81; P < 0.001) observed in women aged < 65 years, women aged ≥ 65, and men, respectively (Table 6).

4. Discussion

In this study, we developed and validated the osteoporosis screening algorithm, COSA, in the Hong Kong Chinese population.

Table 5
The risk reclassification performance of COSA when compared to OSTA.

Group	Category-less NRI			IDI		
	Estimate	95% CI	P-value	Estimate	95% CI	P-value
Women aged <65	0.469	0.259–0.6791	< 0.001	0.028	0.013–0.044	< 0.001
Women aged ≥65	0.578	0.441–0.716	< 0.001	0.015	0.003–0.027	0.012
Men	0.73	0.4348–1.025	< 0.001	0.068	0.009–0.127	0.023

NRI: net reclassification index; IDI: integrated discrimination improvement.

Table 6
Association of COSA with the 10-year risk of incident hip fracture.

Cohort	Group	Sample size, N	Hip fracture, N (%)	OR	95% CI	P-value
Development cohort	Men	745	13 (1.7%)	3.79	(1.22–11.79)	0.022
	Women aged < 65	832	6 (0.7%)	3.54	(0.71–17.68)	0.124
	Women aged ≥ 65	609	41 (6.7%)	4.80	(2.43–9.48)	< 0.001
Validation cohort	Men	729	16 (2.2%)	11.51	(4.16–31.81)	< 0.001
	Women aged < 65	840	4 (0.5%)	4.96	(0.51–47.91)	0.166
	Women aged ≥ 65	630	36 (5.7%)	4.65	(2.24–9.65)	< 0.001

We compared the performance of COSA with OSTA, and found that COSA had a significantly improved reclassification of osteoporosis when compared to OSTA. In an external validation cohort comprising 1876 community dwelling subjects recruited from 2019 to 2021, we showed that the PPV of COSA was 40.6% in women aged < 65, 59.4% in women aged ≥ 65, and 19.4% in men.

To our knowledge, there was only 1 widely validated osteoporosis screening algorithm in Asia, OSTA, which has been validated in Chinese, Indian, Singaporean, and Thai. Among postmenopausal women in Beijing, OSTA has a sensitivity of 69.9%, specificity of 75.1%, PPV of 52.5%, and NPV of 86.2% [10]. For postmenopausal women in a rural area of India, OSTA has a sensitivity of 88.5% and specificity of 41.7% in identifying osteoporosis at the femoral neck [11]. In Singaporeans, a modified cutoff point was used (−1.2) with sensitivity of 76%, specificity of 74%, PPV of 48%, and NPV of 91% [12]. Among middle-aged pre- and early post-menopausal women in Thai, OSTA has a sensitivity of 57.3%, specificity of 76.8%, PPV of 16.34%, and NPV of 95.83% [13]. The overall performance of OSTA in identifying subjects at risk of osteoporosis varied between population, which could be due to study design, rural versus non-rural subjects, age of subjects included, ethnicity, etc. In general, we observed the lowest specificity and highest sensitivity in women aged ≥ 65 years when compared to other studies, which reflects that the cutoff point of −1 identify almost all osteoporosis cases but also include a large number of subjects without osteoporosis. Conversely, COSA has a significantly improved reclassification of osteoporosis in all groups, suggesting that COSA can be used to screen for osteoporosis in Hong Kong Chinese more accurately.

Population-specific risk factors are more important in predicting a clinical outcome. We previously showed that the risk score composed of Hong Kong specific risk factors outperformed the FRAX in predicting hip fracture [14]. In the current study, we included a number of well-established risk factors in identifying subjects with osteoporosis and selected the most robust predictors that passed Bonferroni correction. These factors were consistently and independently associated with osteoporosis in both development and validation cohorts. These could potentially explain why COSA had a higher accuracy when compared to the OSTA, as OSTA was originally developed to assess its applicability in postmenopausal osteoporosis based on a group of Asian women with different ethnicities, the beta estimates of OSTA are more specific for the Asian women, which may be less generalizable to Chinese women. In addition, we previously demonstrated that there was a secular increase in BMD in Hong Kong [15]. Since OSTA was developed in 2001 [4], it is not surprising that the estimates used in OSTA may not be as accurate as COSA, which was developed using the data up to 2010 and accounted for the secular increase in BMD. In addition, we incorporated into COSA the history of fracture, a strong risk factor of osteoporosis and fracture, which could further explain why COSA performed better than OSTA in identification of people with osteoporosis.

The real-world external validation study further demonstrated the usefulness of COSA in population screening of osteoporosis. The PPV of COSA in the internal and external validation was 21.8% vs 19.4% for men, 23.15% vs 42.6% in women aged < 65 years, and 73.46% vs 62% in women aged ≥ 65 years. The PPV observed in women aged ≥ 65 years was ~10% lower than that observed in the internal validation cohort. One of the reasons could be explained by the overlap of recruitment period with the COVID-19 pandemic period, during which the government advocated the elderly to stay home. The potential healthy cohort bias is supported by the lower percentage of participants with COSA > 0 in women aged ≥ 65 years, when compared to women aged < 65 years (Supplementary Table 2). Therefore, we expect that the actual PPV of COSA in women aged ≥ 65 years should be higher than that observed in the current study. In addition, we previously reported a secular increase in BMD in Hong Kong Chinese population [15]. Since the HKOS cohort study was established from 1995 to 2010, it is expected that the BMD in Hong Kong population has been further improved, leading to a lower PPV.

COSA is also a predictor of hip fracture. We showed that women aged ≥ 65 years and men with a COSA > 0 were significantly associated with a substantially higher risk of 10-year hip fracture. Thus, it is possible to use COSA > 0 as a threshold to identify people who have a higher risk of hip fracture. However, the estimates observed varied between development and validation cohorts, which could be because of the small number of events in women aged < 65 and men (Table 6). Conversely, the estimates observed for women aged ≥ 65 were consistent in both development and validation cohorts. Similarly, the null association of COSA with incident hip fracture in women aged < 65 could be due to small event number and hence insufficient statistical power. Adequately powered study in future is required to examine the association of COSA with incident hip fracture in women aged < 65.

The current study has important clinical implications. We recently reported that the global hip fracture burden is increasing even though declining trends in hip fracture incidence were observed in many countries. To reduce the absolute number of hip fracture in the future, more efforts should be put in reducing risk of hip fracture. One possible way is to implement population screening. A previous randomized controlled trial in the United Kingdom showed that a community-based screening intervention reduced hip fracture risk [16]. Thus, our simple tool, COSA, can be used to screen for osteoporosis in the community. Given that DXA availability is limited, our tool can be used to prioritize high-risk subjects for DXA diagnosis. This can reduce the number of people needed for having DXA scan. Moreover, this simple tool can also improve public awareness of osteoporosis and easily implemented by the non-government organizations and used by the users themselves. In addition, COSA > 0 can be used to predict 10-year risk of incident hip fracture in women aged < 65 and men. Thus, these findings suggest the potential use of COSA >0 as a threshold to guide treatment initiation in Hong Kong, despite further study is required.

Our study has several strengths. The HKOS cohort is a well-established cohort study of osteoporosis with a large sample size. Thus, our finding should have a high generalizability to the Hong Kong population. We included both internal and external validation

cohorts, allowing us to evaluate the usefulness of the tool in screening osteoporosis. Nevertheless, there are limitations. First, HKOS was established more than a decade ago as aforementioned, the average BMD in Hong Kong population should have been improved. Thus, the actual sensitivity and specificity should have changed. Further validation study is required to evaluate the actual accuracy of COSA using database or cohorts with more recently collected data. Second, the generalizability to other populations is unknown. Third, although COSA > 0 was shown to be associated with higher 10-year risk of hip fracture in the current study, further study is required to examine if COSA screening can help guiding treatment initiation and preventing hip fracture. Fourth, COSA is more complicated than OSTA. However, the calculation of COSA can be done in an APP or website (like FRAX), which may increase its popularity. Fifth, the sample size of men in this study was small, thus cautious interpretation is required. Future study with a larger sample size is required to further validate our findings.

5. Conclusions

We developed a simple osteoporosis screening algorithm, COSA, for the Hong Kong Chinese population. COSA had a significantly higher accuracy than the existing osteoporosis screening tool, OSTA. COSA > 0 was associated with a higher 10-year risk of hip fracture. Whether COSA can be used to guide treatment initiation and prevent fracture requires further study.

CRediT author statement

Ching-Lung Cheung: Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing – Original Draft, and Writing –Review & Editing. **Gloria HY Li**: Investigation and Writing –Review & Editing. **Hang-Long Li**: Investigation and Writing –Review & Editing. **Constance Mak**: Investigation, Data Curation, and Writing –Review & Editing. **Kathryn CB Tan**: Resources and Writing –Review & Editing. **Annie WC Kung**: Resources, Data Curation, and Writing –Review & Editing.

Conflicts of interest

Ching-Lung Cheung receives honorarium and research support from Amgen Inc. All other authors declare no competing interests.

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Appendix A. Supplementary data

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