# A Probability Formula Derived From Serum Indicators, Age and Comorbidities As An Early Predictor of Dementia For Elderly Chinese People

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**Research Article**

**Keywords:** Total cholesterol, low-density lipoproteins, homocysteine, dementia, elderly, screen

**Posted Date:** February 2nd, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-156565/v1



**Version of Record:** A version of this preprint was published at Brain and Behavior on June 26th, 2021. See the published version at https://doi.org/10.1002/brb3.2236.

# Abstract

**Background:** Blood-based indicators are potential economical and safe methods of population screening for dementia although their predictive values have not been confirmed. The present study proposes a dementia prediction formula based on serum indicators and patient characteristics.

**Methods**: From Jan 2016 to Dec 2018 the data of elderly patients aged over 60 years admitted to the Department of Neurology and Geriatrics in our hospital were retrospectively reviewed. A multivariate logistic regression model was applied to verify the patients' characteristics and serum indicators associated with the risk of dementia. After receiver operating characteristic curve (ROC) and area under the ROC curve (AUC) analysis, we propose a dementia prediction formula and cutoff values for predictive ability of early dementia.

**Results**: 4,722 elderly patients were enrolled and the incidence of dementia was 12.0% (565). When patients had ≥ 8 comorbidities, their risk of developing dementia was 20 times higher than those without comorbidities. After multivariate regression analysis, age (OR: 1.086, $P < 0.001$) and homocysteine concentrations (HCY) (OR: 1.017, $P = 0.003$) were proven to be linked the risk of developing dementia, while total cholesterol (TC) (OR: 0.674, $P = 0.005$) was a protective factor for dementia. We developed a formula of age + LDL-C+ TC + HCY + number of comorbidities as a good predictor of dementia (AUC: 0.79), with a probability (cut-off) value of 0.112 (sensitivity 87.4%, specificity 55.8%, accuracy 60.5%).

**Conclusions:** High serum HCY and low TC were risk factors for developing dementia. A cut-off value > 0.112 derived from the formula of age + LDL-C + TC + HCY + number of comorbidities was an excellent predictor for a high risk of dementia, which may be a potentially useful diagnostic tool for identifying at risk patients using this routine clinical test.


# Background

Dementia is a disease characterized by cognitive decline that affects daily activities and social functioning and is a great challenge for global health and social care in the 21st century [1]. As the world population ages, the incidence of dementia has exponentially increased, particularly in older people. In 2015, it has been estimated that 50 million people had dementia worldwide and by 2050 more than 152 million people are predicted to have this debilitating disease [2]. In China, the incidence in the population of individuals older than 60 years is 7.2% (global average 6.2%), and the annual incidence rate is 0.625%, accounting for approximately 25% of the global total [3, 4]. According to the China Cognition and Aging Study, by 2009 there were 9.2 million people with dementia in China, of which 62.5% were diagnosed with Alzheimer's disease (AD) [5]. Dementia leads to increased costs for governments, communities, families and affected individuals, and results in reduced productivity of the economy. It has been estimated that the annual cost of dementia worldwide is about $818 billion [6, 7]. Existing drugs such as cholinesterase inhibitors and glutamate receptor antagonists can only improve symptoms in the

short term, but do not delay disease progression [8–10]. Therefore, early detection, diagnosis and treatment have become the global consensus of dementia prevention and its treatment.

At the present time, the treatment rate of dementia in China is only 26.9%, with the missed clinical diagnosis rate being as high as 76.8% (for example, 39% greater than in the Netherlands). Ninety-three percent of dementia patients in the community have not been identified (33% higher than in the UK), and the standardized treatment rate is only 21.3% (less than one third of the United States), which means that the overall level of dementia diagnosis and treatment in China lags well behind high-income countries [1, 11]. The Mental State Examination Scale (MMSE) or the Montreal Cognitive Assessment are mainly used to screen for early dementia in China, but scale screening is easily affected by the mental state of the subjects and their surrounding environment, and the assessment accuracy is often poor and follow-ups are required. A more economical and safe method of population screening would be the collection of accessible tissue samples (such as blood) to screen for predictor indicators.

Studies on the association between some common clinical blood test indicators and dementia have increased in recent years. Measurement of serum lipid profiles is a routine and extensive clinical procedure for the diagnosis and guidance of treatment for patients with dementia. Lipid profiles are considered valuable blood-based biomarkers because they are readily modifiable factors to potentially slow or prevent the development of dementia. However, published studies on the association between lipid profiles and the risk of developing dementia have to date produced inconsistent results [12–15]. Similarly, as a modifiable indicator, high levels of homocysteine (HCY) have toxic effects on blood vessels and nerves and are associated with the pathogenesis of dementia [16]. However, the results of epidemiological prospective cohort studies on serum HCY and dementia risk were inconsistent, with some reporting a positive association [17, 18] and others concluding no association [19, 20]. In addition, many investigations have suggested a link between vitamin D deficiency and dementia [21, 22], and that supplementation with vitamin D derivatives may well reduce the risk of dementia [23].

We conducted a large sample real-world study involving 4,722 elderly Chinese patients from Jan 2016 to Dec 2018, in order to identify the risk factors for dementia, including demographic characteristics and common serum indicators. We also aimed to find a dementia prediction formula that could identify elderly patients with a high risk of developing dementia.

# Methods

# Study population

The study was a retrospective analysis of data acquired from dementia and control elderly patients aged ≥ 60 years from Jan 2016 and Dec 2018 who were treated at our hospital the control patients received therapy for a number of other conditions. Exclusion criteria were individuals with liver failure, a serum creatinine concentration > 120 μmol/L, hyperthyroidism or hypothyroidism infections, disorders of the immune system, or on drugs that alter cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-

density lipoprotein cholesterol (HDL-C) concentrations. The diagnosis of dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders [24].

The Institutional Review Board approved the protocols employed and waived the requirement for written informed consent.

# Data collection

We reviewed the medical histories of patients and documented age, gender, comorbidities, and serum parameters (fasting blood glucose (FPG) (mmol/L), HbA1C (mg/dL), total cholesterol (TC) (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), HCY (μmol/L), folic acid (mmol/L), vitamin D2 (mmol/L) and vitamin D3 (mmol/L)). Cardiac disease was defined as a history of: congestive heart failure; myocardial infarction; angina pectoris or medication with digitalis at any time; hypertension, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; use of antihypertensive agents; diabetes, fasting glucose concentration ≥ 7 mmol/L, postprandial glucose or a 2 h 75 g oral glucose post loaded level ≥ 1 mmol/L, insulin or oral hypoglycemic medication; hypercholesterolemia, fasting TC ≥ 6.2 mmol/l or the use of lipid-lowering drugs (statins, fibrate, bile acid sequestrant); lung disease, asthma, COPD, bronchiectasis, pulmonary fibrosis or sarcoidosis; cerebrovascular disease; stroke, transient ischemic attacks, aneurysm or vascular malformations. The history of gastrointestinal disorders refers to the esophagus, stomach, small intestine, large intestine, rectum, pancreas gallbladder and liver). Nephrosis was defined as a urine test for the presence of protein, a blood test for lower-than-normal levels of protein, and the clinical detection of edema. A history of fracture was defined as a break in any bone or cartilage. Cancer was defined by a medical history of cancer.

# Measurements of serum indicators

Fasting venous blood samples (3 mL and 4 mL) were collected into tubes containing EDTA-K2 anticoagulant and vacuum separated gel blood collection vessels, respectively and stored at -80°C for subsequent testing. FPG, TC, HDL-C, LDL-C, HCY, folic acid, vitamin D2 and vitamin D3 concentrations were measured with an Advia Clinical Chemistry System (Siemens Healthcare, Erlangen, Germany).

# Statistical analysis

SPSS ver. 23 (IBM, US) was employed to analyze all datasets. Discrete data are given as numbers or percentages and continuous data with a normal distribution as the mean ± SD. To analyze potential risk factors affecting dementia uni- and multivariate linear regression was employed. Data are given with 95% confidence intervals (CI). The predictive ability of indicators for dementia was evaluated by receiver operating characteristic (ROC) analysis. The cut-off values for indicators were determined by ROC analyses (Youden Index). A statistically significant finding was deemed to be a two-sided *P*-value < 0.05.

## Results

# Patient characteristics and baseline information

A total of 4,722 elderly patients were included, with an average age of 73.0 ± 15.5 years, and 52.5% were male. Most of the patients were in the Department of Neurology (77.8%). There were 565 patients with dementia, with an incidence rate of 12%. Cerebrovascular disease, hypertension and heart disease were the top 3 comorbidities, accounting for 74.2%, 59.5% and 38.9%, respectively (**shown in** Table 1).

Table 1
General characteristics of the patients

| Variables | | Patients (n = 4,722) |
|---|---|---|
| Gender | Male | 2,479 (52.5) |
| | Female | 2,243 (47.5) |
| Age | | 73.0 ± 15.5 |
| Medical department | Neurology | 3,672 (77.8) |
| | Geriatrics | 1,050 (22.2) |
| Diagnosis | Dementia | 565 (12.0) |
| | Non-dementia | 4,157 (88.0) |
| Comorbidities | Cerebrovascular disease | 3,502 (74.2) |
| | Hypertension | 2,811 (59.5) |
| | Heart disease | 1,839 (38.9) |
| | Diabetes | 1,192 (25.2) |
| | Lung disease | 1,123 (23.8) |
| | Hyperlipidemia | 319 (6.8) |
| | Tumor | 206 (4.4) |
| | History of fracture | 84 (1.8) |
| | Chronic kidney disease | 84 (1.8) |
| | Gastrointestinal diseases | 10 (0.2) |
| Serum indicators | FBG (mmol/L) | 5.9 ± 2.5 |
| | HbA1C (mg/dL) | 6.3 ± 1.3 |
| | TC (mmol/L) | 4.3 ± 1.1 |
| | HDL-C (mmol/L) | 1.2 ± 0.3 |
| | LDL-C (mmol/L) | 2.3 ± 0.8 |
| | HCY (μmol/L) | 17.2 ± 10.5 |
| | Folic acid (mmol/L) | 8.5 ± 5.0 |
| | Vitamin D2 (mmol/L) | 1.7 ± 3.3 |

Note: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; HCY, homocysteine; HbA1C, hemoglobin A1C; TC, total cholesterol

| Variables | Patients (n = 4,722) |
|---|---|
| Vitamin D3 (mmol/L) | 14.1 ± 8.0 |

Note: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; HCY, homocysteine; HbA1C, hemoglobin A1C; TC, total cholesterol

# Univariate analysis of the general characteristics of dementia

Dementia patients were significantly older than non-dementia patients, but there was no difference in gender. Lung disease (OR: 1.411, $P < 0.001$), fracture (OR: 1.202, $P < 0.001$), heart disease (OR: 1.123, $P < 0.001$), hypertension (OR: 1.120, $P < 0.001$) and cerebrovascular disease (OR: 1.080, $P < 0.001$) were linked with a higher risk for the incidence of dementia. However, diabetes did not increase the risk of developing dementia. From the perspective of the number of comorbidities, OR increased with the number of comorbidities. When patients had ≥ 8 comorbidities, their risk of developing dementia was 20 times higher than those without comorbidities. Even 2 to 3 comorbidities increased the odds of dementia by a factor of 7.75. On the other hand, hyperlipidemia was the only indicator we found that was negatively linked to dementia risk (OR: 0.767, $P < 0.001$) (**shown in** Table 2).

Table 2
Univariate analysis of gender, age and comorbidities for dementia

| | | Dementia (n = 565) | Non-dementia (n = 4,157) | OR (95% CI) | *P*-value |
|---|---|---|---|---|---|
| **Gender** | Male | 301 (53.3) | 2,178 (52.4) | 1.0 | 0.694 |
| | Female | 264 (46.7) | 1,979 (47.6) | 0.965 (0.809–1.151) | |
| **Age** | | 85.9 ± 8.3 | 71.2 ± 15.4 | 1.122 (1.109–1.135) | < 0.001 |
| **Lung disease** | No | 361 (63.9) | 3,238 (77.9) | 1.0 | |
| | Yes | 204 (36.1) | 919 (22.1) | 1.411 (1.285–1.549) | < 0.001 |
| **Hypertension** | No | 189 (33.5) | 1,722 (41.4) | 1.0 | |
| | Yes | 376 (66.5) | 2,435 (58.6) | 1.120 (1.053–1.192) | < 0.001 |
| **Hyperlipidemia** | No | 550 (97.3) | 3,853 (92.7) | 1.0 | |
| | Yes | 15 (2.7) | 304 (7.3) | 0.767 (0.672–0.875) | < 0.001 |
| **History of fracture** | No | 544 (96.3) | 4,094 (98.5) | 1.0 | |
| | Yes | 21 (3.7) | 63 (1.5) | 1.202 (1.087–1.329) | < 0.001 |
| **Chronic kidney disease** | No | 557 (98.6) | 4,081 (98.2) | 1.0 | |
| | Yes | 8 (1.4) | 76 (1.8) | 0.958 (0.847–1.082) | 0.488 |
| **Cerebrovascular disease** | No | 100 (17.7) | 1,120 (26.9) | 1.0 | |
| | Yes | 465 (82.3) | 3,037 (73.1) | 1.080 (1.046–1.116) | < 0.001 |
| **Diabetes** | No | 422 (74.7) | 3,108 (74.8) | 1.0 | |
| | Yes | 143 (25.3) | 1,049 (25.2) | 1.0 (0.976–1.026) | 0.969 |

| | | Dementia (n = 565) | Non-dementia (n = 4,157) | OR (95% CI) | *P*-value |
|---|---|---|---|---|---|
| **Gastrointestinal diseases** | No | 565 (100) | 4,147 (99.8) | 1.0 | |
| | Yes | 0 (0) | 10 (0.2) | 0.258 (< 0.001->999.9) | 0.975 |
| **Heart disease** | No | 205 (36.3) | 2,678 (64.4) | 1.0 | |
| | Yes | 360 (63.7) | 1,479 (35.6) | 1.123 (1.102–1.143) | < 0.001 |
| **Tumor** | No | 548 (97) | 3,968 (95.5) | 1.0 | |
| | Yes | 17 (3) | 189 (4.5) | 0.962 (0.919–1.007) | 0.096 |
| **Number of comorbidities** | 0 | 3 (0.5) | 376 (9.0) | 1.0 | |
| | 2–3 | 12 (2.1) | 194 (4.7) | 7.75 (2.16–27.76) | 0.002 |
| | 4–5 | 3 (0.5) | 43 (1.0) | 8.74 (1.71–44.63) | 0.009 |
| | 6–7 | 27 (4.8) | 393 (9.5) | 8.60 (2.59–28.58) | < 0.001 |
| | 8–9 | 24 (4.2) | 124 (3.0) | 24.24 (7.18–81.84) | < 0.001 |
| | ≥ 10 | 496 (87.7) | 3,027 (72.8) | 20.52 (6.57–64.13) | < 0.001 |

# Univariate analysis of serum indicators for dementia

We also compared serum indicators in patients with and without dementia. The risk of the incidence of dementia was reduced with higher concentrations of total cholesterol (OR: 0.804, $P < 0.001$), LDL-C (OR: 0.743, $P < 0.001$) and Vitamin D3 (OR: 0.982, $P = 0.015$), whereas it increased with higher concentrations of HCY (OR: 1.012, $P = 0.017$) (**shown in** Table 3).

Table 3
Analyses of biomarkers for risk of dementia (n = 4,722)

| | Dementia (n = 565) | Non-dementia (n = 4,157) | OR (95% CI) | *P*-value |
|---|---|---|---|---|
| **Univariate analysis** | | | | |
| FBG (mmol/L) | 6.1 ± 2.6 | 5.9 ± 2.5 | 1.021 (0.986–1.057) | 0.244 |
| HbA1C (mg/dL) | 6.3 ± 1.2 | 6.3 ± 1.3 | 0.953 (0.879–1.032) | 0.236 |
| TC (mmol/L) | 4.1 ± 1.1 | 4.4 ± 1.1 | 0.804 (0.734–0.881) | < 0.001 |
| HDL-C (mmol/L) | 1.2 ± 0.4 | 1.2 ± 0.3 | 0.939 (0.712–1.239) | 0.657 |
| LDL-C (mmol/L) | 2.1 ± 0.7 | 2.3 ± 0.8 | 0.743 (0.653–0.844) | < 0.001 |
| HCY (μmol/L) | 18.5 ± 10.3 | 16.9 ± 10.5 | 1.012 (1.002–1.021) | 0.017 |
| Folic acid (mmol/L) | 8.3 ± 5.5 | 8.5 ± 5.0 | 0.992 (0.971–1.013) | 0.454 |
| Vitamin D2 (mmol/L) | 1.9 ± 3.4 | 1.6 ± 3.3 | 1.022 (0.994–1.051) | 0.131 |
| Vitamin D3 (mmol/L) | 13.1 ± 8.3 | 14.2 ± 7.9 | 0.982 (0.967–0.996) | 0.015 |
| **Multivariate analysis** | | | | |
| Age | | | 1.086 (1.067–1.105) | < 0.001 |
| TC | | | 0.674 (0.513–0.885) | 0.005 |
| HCY | | | 1.017 (1.006–1.028) | 0.003 |

Note: FBG, fasting blood glucose; HbA1C, Hemoglobin A1C; TC, total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HCY, homocysteine

# Multivariate analysis of general characteristics and serum indicators for dementia

Our multivariate regression analysis proved that age (OR: 1.086, $P < 0.001$) and HCY concentrations (OR: 1.017, $P = 0.003$) were risk factors for developing dementia, while TC (OR: 0.674, $P = 0.005$) was a protective factor against developing this condition (**shown in** Table 3).

The predictive ability of LDL-C, TC, HCY concentrations and their combinations with age and the number of comorbidities in predicting dementia

We performed receiver operating characteristic analysis of a large group of patients (n = 4,722) and found that age + LDL-C + TC + HCY + number of comorbidities was a good predictor of dementia (AUC: 0.79), with a cutoff value of 0.112 (sensitivity 87.4%, specificity 55.8%, accuracy 60.5%) **(shown in** Table 4, **Figure. 1)**.

Table 4
The cut-off value, sensitivity, specificity and accuracy of serum indicators and their combination with patient characteristics to predict dementia in ROC analysis

| | Cut-off value | Sensitivity (%) | Specificity (%) | Accuracy (%) | ROC |
|---|---|---|---|---|---|
| LDL-C | 2.18 | 58.1 (53.7–62.5) | 53.0 (51.4–54.6) | 53.6 (52.1–55.1) | 0.54 (0.51–0.58) |
| TC | 4.15 | 56.4 (51.9–60.7) | 55.4 (53.8–57.1) | 55.6 (54.0-57.1) | 0.57 (0.53–0.60) |
| HCY | 14.5 | 61.0 (55.4–66.4) | 52.5 (50.2–54.8) | 53.7 (51.6–55.8) | 0.57 (0.54–0.60) |
| LDL-C + HCY | 0.154 | 44.5 (38.9–50.1) | 66.4 (64.2–68.6) | 63.2 (61.1–65.2) | 0.56 (0.53–0.60) |
| TC + HCY | 0.156 | 49.2 (43.6–54.9) | 65.5 (63.2–67.6) | 63.1 (61.0-65.1) | 0.58 (0.55–0.62) |
| LDL-C + TC + HCY | 0.144 | 64.0 (58.5–69.3) | 51.0 (48.7–53.4) | 53.0 (50.8–55.1) | 0.59 (0.56–0.62) |
| LDL-C + TC + HCY + number of comorbidities | 0.155 | 59.9 (54.5–65.3) | 57.1 (54.8–59.3) | 57.5 (55.4–59.6) | 0.61 (0.58–0.64) |
| Age + LDL-C + TC + HCY | 0.126 | 83.9 (79.9–88.0) | 58.7 (56.4–60.9) | 62.4 (60.3–64.4) | 0.79 (0.76–0.81) |
| Age + LDL-C + TC + HCY + number of comorbidities | 0.112 | 87.4 (83.7–91.0) | 55.8 (53.6–58.1) | 60.5 (58.4–62.5) | 0.79 (0.76–0.81) |

Note: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HCY, homocysteine; AUC, area under the curve

We developed a formula: (P = exp (-10.2858 + 0.1074 × age + 0.3922 × LDL - C-0.3901 × TC + 0.0113 × HCY + 0.0785 × number of comorbidities) / (1 + exp (-10.2858 + 0.1074 × age + 0.3922 × LDLC − 0.3901 × TC + 0.0113 × HCY + 0.0785 × number of comorbidities))) as be used to identify patients that were at an increased risk of developing dementia. These results indicated that a combination of age + LDL-C + TC + HCY + number of comorbidities may be a potential candidate formula to predict dementia.

# Discussion

In the present study, high HCY concentrations and low TC levels were closely related with the risk of developing dementia among Chinese elderly people. In view of the need for blood-based screening to identify people most at risk of developing this condition, our study has proposed a formula (including age, LDL-C, TC, HCY and number of comorbidities) as a predictive tool to screen out patients with a higher risk of developing dementia at the community level, thus providing the basis for further accurate diagnosis.

As a result of the analysis of the general characteristics of patients, we found that age was a risk factor that was uncontrollable. Age was clearly the biggest risk factor for developing dementia, and most patients with sporadic dementia start to get ill after the age of 65 years. Epidemiological studies [4] in different countries worldwide have confirmed that the incidence and prevalence of dementia increases with age. The results of a meta-analysis revealed that the incidence of dementia doubled every 10 years after the of age 60 years [25]. It is worth noting that dementia is not the inevitable result of aging, and aging itself is not the only reason for the development of dementia.

Vascular risk factors are considered to be important indicators of dementia prevention [26]. Since lipid components represent potential prevention targets that are relatively easy to modify, it is of great clinical importance to explore their relationship with the risk of dementia. To date, studies on any link between dyslipidemia and dementia have produced inconsistent results. The age at which a patient's blood lipid levels are measured, and the length of follow-up may explain these differences. High cholesterol levels were shown to increase the risk of dementia, primarily in studies that measured lipid levels in middle age and/or followed the subjects over time until late in their lives. In contrast, short-term follow-up blood lipid measurement studies of patients in old age or those who did not reach this age with the highest prevalence of dementia, either found no association [14, 27] or sometimes an inverse relationship with the risk of dementia [28, 29]. Our study found that TC was a protective factor for dementia in a large sample of elderly people, and that low TC levels increased the risk of developing dementia. Cholesterol is one of the most important components of neurons and is essential for the development and maintenance of neuronal plasticity and functions [30]. Low cholesterol concentrations may be a symptom of dementia progression [31] and may herald the onset of dementia [32]. Even a drop in the cholesterol concentration, 9 years before dementia developed, can affect the diagnosis [29]. Total cholesterol levels may be reduced over time, but the rate of decline was much greater in patients who eventually experienced impairment of cognition [33]. In addition, a high total cholesterol concentration is associated with a lower mortality of older people [34], and it can thus be speculated that raised cholesterol concentrations give rise to better health than in people who have low cholesterol levels. In particular, these people may have better liver functions because a low total cholesterol concentration may reflect liver disease [34]. Several studies in Chinese populations also support this view [35, 36].

Previously published literature has reported that high HCY levels are independent risk factors for cognitive dysfunction, cerebrovascular disease and atherosclerosis [37]. High levels of HCY have been linked with an elevated risk of individuals developing cardiovascular disease and all-cause deaths [38], but the relationship between HCY and dementia or cognitive deterioration has not been consistently

demonstrated [39]. Our study found that high HCY concentrations is a risk factor for dementia, which is consistent with the results of previous domestic and foreign studies [40]. Increased HCY concentrations may be associated with cognitive decline and the mechanisms involved may be related to direct neurotoxic or cerebrovascular damage. An increased concentration of HCY induces a cascade stress response, leading to intracranial arteriolosclerosis, which eventually induces an insufficient cerebral blood supply that leads to atrophy of the brain. High HCY concentrations can improve the sensitivity of neurons to excitatory poisons, promote apoptosis of neurons, and affect nerve conduction [41]. Interestingly, a recent cross-sectional study [42] found that both low and high cholesterol concentrations might be harmful to cognitive health in people with normal HCY levels. However, in people with high HCY concentrations, homocysteine has an overwhelming effect on cognition, regardless of the cholesterol concentration. This finding suggests that cholesterol and homocysteine may interact in the cognitive functions of an aged population. Both cholesterol and HCY concentrations can effectively be controlled by existing drugs. In 2012, the US Food and Drug Administration (FDA) added possible cognitive adverse reactions (including memory problems) to statin prescription information [43]. In terms of the risk of dementia, the cholesterol-lowering drugs commonly used in the elderly should be taken with caution.

Dementia is a global epidemic and early detection of patients at risk of dementia has become an internationally recognized priority. Blood-based predictive indicators are attractive options in the clinic because they are safe, reliable, simple to use and less costly for screening. For the screening of AD, a number of blood-based biomarkers have initially demonstrated the efficacy of distinguishing AD from matched controls in the elderly. Neocortical Aβ (extracellular β-amyloid) burden (NAB) is a good predictor of the progress of AD. One study recommended predicted human NAB level measurements based on the molecular characteristics of blood (sensitivity: 79.6%, specificity: 82.4%, AUC: 87.6%) [44]. In addition, it was also found that the success rate of MMSE and 25(OH)D3 combination in predicting mild cognitive impairment (MCI) and AD reached 98% [45], suggesting that this combination can support the clinical diagnosis of MCI and mild medium and serious stages of AD. Our study has proposed a formula based on blood test indicators to predict dementia (sensitivity 87.4%, specificity 55.8%, AUC 79%). This formula is simple and easy to use. The blood test indicators (TC, LDL-C and HCY) contained in the formula are low-cost routine tests. The prediction formula can be used as a screening tool for a broad population at the community level to facilitate the identification of patients who could potentially benefit from further more invasive or more expensive confirmatory tests for diagnosis (such as cerebrospinal fluid analysis or PET).

There are a number of limitations to our research that should be considered. First, the patients in our study were all Han people who live in Shanghai. Although this study analyzed a large cohort of patients, caution is needed when extending our conclusions to patients of other races and cities. Second, we made no comparisons between the different clinical types and different levels of cognitive impairment of dementia. Third, there may be a reverse causal relationship between lipid levels and dementia, and patients with dementia may be more likely to suffer from eating disorders and malnutrition, which may lead to lower cholesterol levels in the body. Unfortunately, the design of a cross-sectional study makes it impossible to explore causality. Further prospective studies are needed to provide evidence of causality.

In conclusions, this real-world cross-sectional study of a large sample size found that high HCY concentrations and low TC concentrations were independent risk factors for dementia in elderly patients. The formula of age + LDLC + TC + HCY + number of comorbidities predicted dementia and may serve as a cost-effective tool for the early detection of those people at a risk of developing dementia, and who could benefit from further invasive or indeed expensive confirmatory tests.

# Abbreviations

AD, Alzheimer's disease; AUC, area under the ROC curve, FPG, fasting blood glucose, HCY, homocysteine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAB, Neocortical Aβ (extracellular β-amyloid) burden; MCI, mild cognitive impairment; MMSE, Mental State Examination Scale; ROC, receiver operating characteristic curve; TC, total cholesterol

# Declarations

### Ethics approval and consent to participate

The study was performed according to the principles of the Declaration of Helsinki with regard to ethical research involving human subjects and approved by the Institutional Review Board of the Shanghai Xuhui Central Hospital (No. 2020-201), which waived the requirement of written informed consent.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that there is no conflict of interests in this study.

### Funding

None.

### Authors' contributions

All authors were responsible for the conception and design of the study. QG, MB and LY were responsible for acquisition and analysis of data; furthermore, all authors were in charge of statistical analysis. QG, MB and LY drafted the manuscript; LX revised and commented the draft, and all authors read and approved the final version of the manuscript.

**Acknowledgements**

Not applicable.

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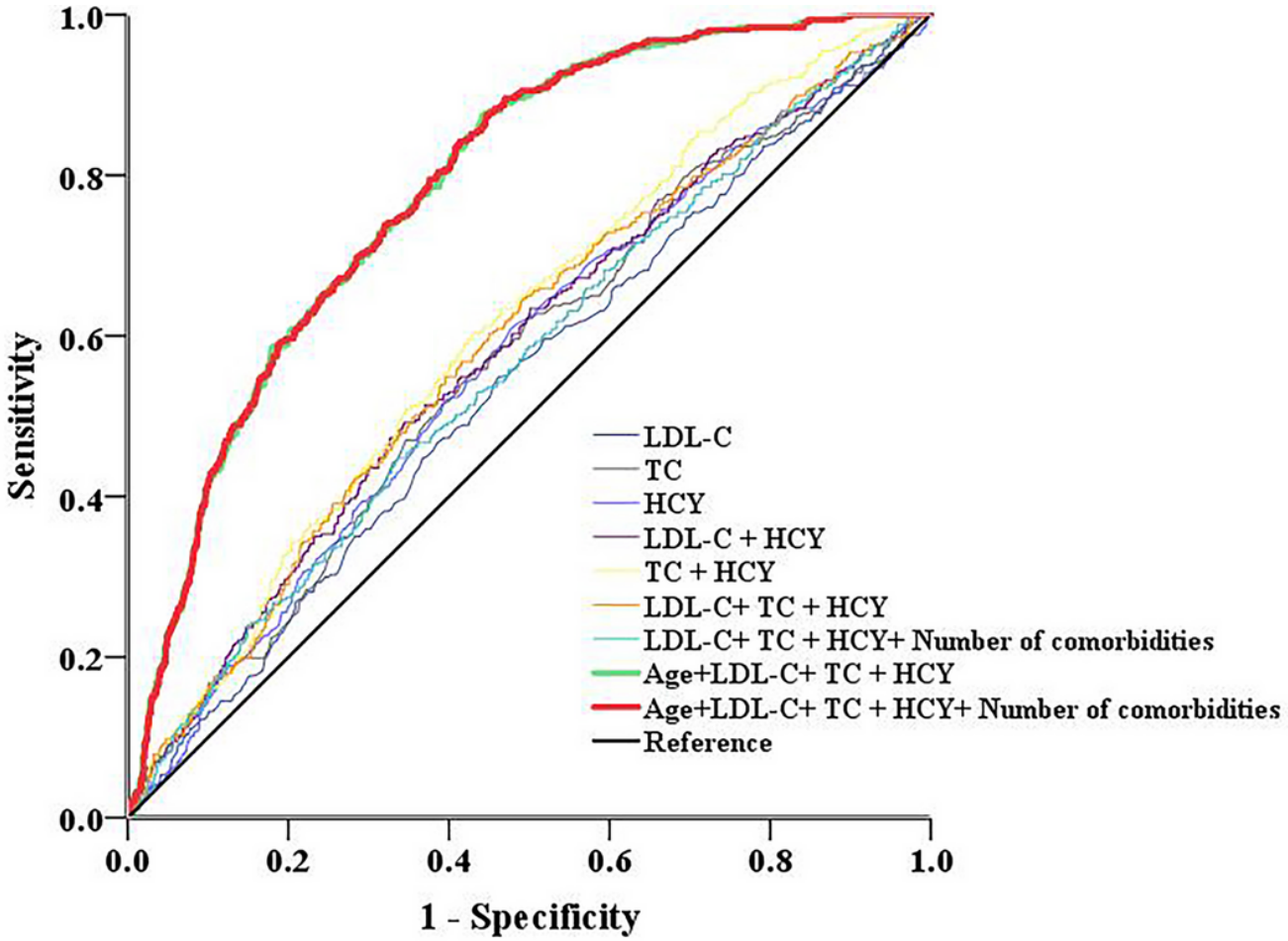
# Figures




## Figure 1

ROC curves of the predictive models of dementia in elderly patients. Note: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HCY, homocysteine