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The influence of baseline platelet on mortality risk in stroke and cancer patients: a cross-sectional analysis of the NHANES database

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Abstract

Background Platelet count and function may be closely related to survival and prognosis of stroke and cancer. However, little is known on the impact of platelet count on the patients with a history of stroke and cancer. This study aimed to examine the association between baseline platelet level and all-cause mortality in this population using a cross-sectional analysis.

Methods Participants with a history of stroke and cancer were selected from the database of the National Health and Nutrition Examination Survey from 2007 to 2018. A maximum selected rank statistic was conducted to determine platelet cutoff with the most significant association with mortality. The association between platelet and mortality was characterized visually using restricted cubic spline (RCS). Weighted multivariable Cox regression models were performed to evaluate the association between platelet count and mortality. Time-dependent receiver operating characteristic (ROC) analysis was conducted to assess the accuracy of platelet count in predicting mortality.

Results Forty-three (43/113, 38.05%) stroke patients with cancer were alive at a median follow-up of 42 months (interquartile range, 23–74 months). The RCS analysis demonstrated a linear relationship between platelet and mortality (nonlinear, $p=0.352$). Mortality in higher-platelet group ($>209\times10^9$/L, $n=57$) was decreased than lower-platelet group ($\leq209\times10^9$/L, $n=56$) (Model 1 HR 0.43, 95% CI 0.24—0.77, $p=0.005$) (Model 2 HR 0.58, 95% CI 0.35—0.96, $p=0.03$). Subgroup analyses showed no significant interaction between platelet and age, sex, BMI, WBC and neutrophil. The areas under time-dependent ROC curve of the 1-, 2-, 3-, 4- and 5-year survival rates were 0.54, 0.55, 0.57, 0.53, 0.59 for mortality of stroke patients with cancer.

Conclusions Lower platelet count may be an independent predictor of all-cause mortality in population with a history of stroke and cancer. This result may provide valuable insights for the long-term management in stroke patients with cancer.

Keywords Stroke, Cancer, Platelet, All-cause mortality, Prognosis

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Introduction

Stroke is a leading cause of death, with its incidence and mortality rates on the rise in China annually. In 2020, the incidence of stroke was 5.05‰, nearly double the 2013 rate of 2.47‰. The mortality rate also witnessed a sharp increase, reaching 3.43‰ in 2020, as opposed to 1.15‰ in 2013 [1, 2]. Studies have shown that there is an increased risk of cancer-associated stroke [3] due to coagulation abnormalities resulting from the cancer itself or its treatment [4, 5]. Apart from atherosclerotic cerebrovascular diseases, tumor-related ischemic stroke can also be caused by abnormal coagulation, tumor-related immune mechanisms, non-bacterial thrombotic endocarditis (NBTE), and disseminated intravascular coagulation. Additionally, hypertensive hemorrhage, intratumoral hemorrhage, and coagulopathies are common mechanisms of cerebral hemorrhage in cancer patients [6]. The anatomical-pathological study carried out on 3,426 cancer patients showed that 14.6% of the individuals had cerebral vascular disease, with clinical symptoms in 51% of cases [3]. In solid tumor patients, the incidence of ischemic stroke (54.1%) is higher than hemorrhagic stroke, whereas in leukemia patients, the incidence of cerebral hemorrhage (72.4%) was significantly higher than cerebral infarction [3]. Moreover, having cancer has been identified as an independent risk factor for a poor prognosis following a stroke [7], with approximately 27.5% of cancer patients experiencing recurrent stroke events [8]. Additionally, stroke patients with a history of cancer tend to have more severe neurological deficits upon admission, worse modified Rankin Scale scores at discharge [4], and higher in-hospital mortality (31.9% vs. 12.5%) [9]. These patients also have a significantly elevated risk of overall mortality. Identifying risk factors is crucial for optimizing clinical management of stroke patients with cancer.

In contrast to traditional etiology, coagulation abnormalities linked to cancer cell-derived extracellular vesicles play a significant role in the pathological processes of cancer-associated stroke [10]. Numerous studies have revealed that increased D-dimer, C-reaction protein levels and mean platelet volume are independent indicators of a poor prognosis [11–13]. Additionally, cancer-related stroke patients often experience a reduction in platelet count during the acute phase of stroke, especially those with multiple arterial thromboembolism, multi-regional stroke, or recurrent stroke within a short period [14]. Platelets, crucial components of blood, play essential roles in hemostasis and immune response. The proliferation and metastasis of tumor cells, along with their interaction with the host immune system, can significantly impact platelet production and survival. Thrombocytopenia, a common hematological complication in cancer patients [15], is often the result of a complex interplay between tumor biology and host responses [16]. Tumor cells can directly affect hematopoiesis in the bone marrow, leading to reduced platelet production, while the immune response to tumors can increase the risk of platelet elimination by altering their living environment [17].

A recent retrospective study showed that stroke patients in cancer group exhibited a reduced platelet count compared to those without cancer [14]. Cancer patients with the lower levels of platelet exhibited poorer mRS scores, suggesting a possible correlation between platelet and prognosis [4]. A subgroup analysis of the China National Stroke Registry (CNSR) II study revealed a significant correlation between platelet levels and mortality as well as prognosis in patients suffering from acute stroke [18]. The study also observed a J-shaped relationship between baseline platelet counts and clinical outcomes in patients with ischemic stroke or TIA, with both higher and lower platelet counts associated with a risk of poor function. It was also noted that the platelet count at the time of the stroke could influence the prognosis of the stroke and the early neurological deterioration of the patient [19]. However, the impact of baseline platelet levels on the population with a history of stroke and cancer is not yet fully understood. This retrospective study aimed to investigate the potential association between baseline platelet levels during non-acute phase of stroke and all-cause mortality in this population.

Methods

Study population

National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm) is a research project established by United States Centers for Disease Control (CDC) and the National Center for Health Statistics (NCHS). The objective of NHANES is to comprehensively evaluate the health of a representative sample of the United States population after survey weighting. In brief, NHANES randomly selects 5,000 individuals annually from all 50 states to represent the national demographic. These individuals are performed demographic analysis based on age, race, income and etc. using a combination of methods, including interviews and questionnaire. The sampled individuals completed their health assessments including laboratory tests and imaging examinations at different times throughout the survey year. All participants were required to sign an informed consent form approved by the Ethics Review Board of the National Center for Health Statistics (Protocol #2005–06, Protocol #2011–17, and Protocol #2018–01).

Data for our study were selected from six cycles of the NHANES database, which included a total of 59,842 participants from 2007 to 2018. Eligible participants for this study including patients aged 18 or over with diagnosis of both stroke and cancer. All enrolled participants must have specific results of platelet count and survival information. Participants without platelet counts and survival information were excluded from further analysis (Fig. 1).

Definitions of stroke and cancer

The information for diagnosis of stroke and cancer was obtained from the questionnaire of the NHANES database conducted in the survey year. We obtained the age of the patient's stroke or tumor diagnosis from the questionnaire and calculated the specific intervals between these diagnoses and the platelet examination. Cancer patient is defined in the NHANES questionnaire: "Has a doctor or other health professional ever told you that you have cancer, and what kind of cancer did you have?" (Supplement questionnaire: MCQ_2007-2017) The neoplasms included tumors of the respiratory system, digestive system, reproductive system, hematopoietic system, skin, and other types. Stroke patients are defined in the NHANES questionnaire: "Have you ever been told you had a stroke?" (Supplement questionnaire: MCQ_2007-2017) However, the NHANES database lacks detailed information regarding the types of strokes.

Survival and mortality outcomes of the participants

Survival information of participants was obtained from the National Death Index (NDI) database of NHANES (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). The International Statistical Classification of Diseases, 10th Revision (ICD-10) was used to define causes of death. All-cause mortality category included deaths resulting from cancer (C00-C97), cardiovascular disease (I00-I09, I11, I13, I20-I51), cerebrovascular disease (I60-I69), respiratory disease (J10-J18, J40-J47), and other causes (Supplement questionnaire: mortality files_2019). For each individual, the follow-up period concluded at the time of death or on 31 December 2019, which was the final follow-up date. In this study, survival was defined as being alive for at least 60 months since interviewed time, while being alive for less than 60 months was considered to be death.

Covariates

In order to comprehensively evaluate the impact of covariates on the outcome, a number of potential covariates were carefully selected for consideration. Demographic factors and health questionnaire was used to obtain gender, age, race (Mexican American, non-Hispanic White, non-Hispanic Black, and others) (Supplement questionnaire: DIQ_2007-2012), educational level (Less than high school, High school or equivalent, and College or above) (Supplement questionnaire: DMQ_Family_2007-2011), family income-poverty ratio (Supplement questionnaire: INQ_Family_2007-2017), smoking history (NO. SMQ020 "Smoked at least 100 cigarettes in life", Yes or No) (Supplement questionnaire: SMQ_ 2007–2017), and alcohol history (NO. ALQ110 "Had at least 12 alcohol drinks/lifetime?" Yes or No) (Supplement questionnaire: ALQ_

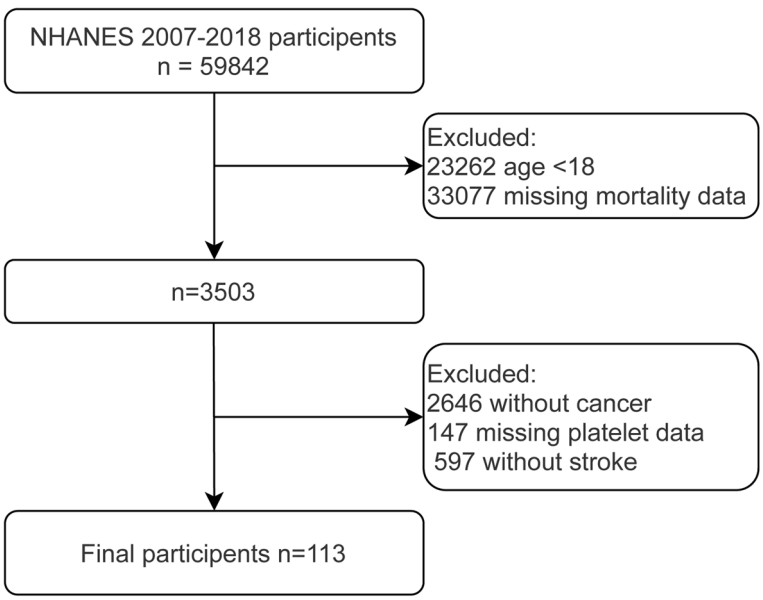

Fig. 1 The flow chart illustrated the criteria for inclusion and exclusion of the participants

2005–2013). Physical data, including height and weight, was available for all participants. Body mass index (BMI) was calculated using the formula: BMI = kg/m^2. The participants themselves reported histories of hypertension, diabetes, and coronary heart disease in the questionnaire. A series of laboratory tests results were obtained for participants, including serum levels of high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol, triglyceride, glycosylated hemoglobin (HbA1c), white blood cell, red blood cell, lymphocyte, neutrophil and hemoglobin. Continuous variables included age, family income-poverty ratio, BMI, HDL, LDL, total cholesterol, triglyceride, HbA1c, white blood cell, red blood cell, lymphocyte, neutrophil and hemoglobin. Categorical variables concluded sex, race, educational level, smoking history, and alcohol history, hypertension history, diabetes history, and coronary heart disease history.

Statistics analysis

In order to create multiple complete datasets and reduce statistical error, multiple imputation was employed to address the presence of missing data before subsequent analysis. In the context of multiple imputation, multiple plausible values for specific variables were estimated for each individual with missing data (Supplementary Fig. S1-S2; supplementary Table). We conducted statistical analyses by applying appropriate survey weights to make the estimates reported here nationally representative of the United States civilian non-institutionalized adult population. Sample weight was calculated as: fasting 12-year mobile examination center (MEC) weight = fasting 2-year MEC weight/6. Continuous variables were characterized as mean values and 95% confidence intervals, while categorical variables were represented by percentages and 95% confidence intervals. Continuous variables were compared between groups using the Student *t* test and the Mann–Whitney *U* test. The differences of classified variables between two groups were analyzed by the chi-square test. The greatest significant impact on survival outcome was determined by the most appropriate cutoff point of platelet count which was obtained through the maximum selected rank statistics (MSRS) method. Participants were then divided into lower and higher-platelet groups according to MSRS results. Both of the two groups conducted analysis upon a sample size between a minimum of 25% of the total and a maximum of 75%.

The possible nonlinear relationship between platelet count and all-cause mortality in stroke patients with cancer was visualized by the restricted cubic splines (RCS) with four knots. Survey-weighted Cox regression analysis was employed to assess linear correlation between platelet count and all-cause mortality. Two models were constructed for adjusting the potential confounding factors. Given the small sample size of 113 cases, the overfitting phenomenon may occur if all covariates were controlled for the models. Model 1 controlled age, gender, race, family income-poverty ratio, educational level, alcohol history, smoke history, hypertension, diabetes, coronary heart disease, HbA1c, BMI, HDL, LDL, total cholesterol, triglyceride, white blood cell, red blood cell, lymphocyte, neutrophil and hemoglobin. Model 2 was adjusted for the variables age, gender, BMI, white blood cell and neutrophil that have the highest correlation coefficient. The survival outcomes of two groups were visualized by Kaplan–Meier survival curves and the statistical comparison was conducted by the log rank test. Subgroup analysis was conducted to evaluate the relationship of platelet count with all-cause mortality based on adjustment of age, gender, BMI, white blood cell and neutrophil. Time-dependent receiver-operating characteristic curve (ROC) analysis was conducted to assess the predictive accuracy of platelet levels at various time points in relation to all-cause mortality. The data analysis was performed using R Statistical Software, version 4.2.3. A two-tailed *p*-value of less than 0.05 indicated statistically significant difference.

Results

Demographic Characteristics and hemodynamic indexes of the study population

Out of 59,842 participants, 3,503 over the age of 18 provided information on their survival status. Among the 3,503 participants, 260 had a history of both tumors and strokes. Due to missing data of the platelet count, 147 participants were excluded for not meeting the inclusion criteria. The present study ultimately enrolled a total of 113 eligible participants with complete data on platelet count and survival status, representing 275504 patients with stroke and cancer in the United States (Fig. 1).

The median intervals between stroke diagnoses and the platelet examination was 6 years (Interquartile Range (IQR), 13 (1–14) years) (Supplement Fig. S3). The median intervals between cancer diagnoses and the platelet examination was 8 years (IQR, 13.5 (2.75–16.25) years) (Supplement Fig. S4). The study found that 66% of patients had been diagnosed with a cancer over 5 years ago, indicating most were long-term survivors. Among the participants, one individual was found to have a platelet count of below 100×10^9/L, while the rest had platelet counts within the normal range $100 \sim 450 \times 10^9$/L. Because NHANES uses a representative survey to gather health and dietary data from individuals, the platelet detection readings in this study are mainly representative of stroke patients who are in the post-acute stage.

Multiple imputation was used to generate multiple complete datasets and lower statistical error since significant stroke risk factors, such as alcohol history (67.23%), LDL (47.49%), and TG (46.9%), had more missing values. The MSRS indicated an optimal cutoff point of platelet count of 209×10^9/L, which corresponding to the most significant association with survival status of stroke patients with cancer (Fig. 2A). These participants were subsequently divided into the lower-platelet group (platelet $\leq 209\times10^9$/L, n = 56), and the higher-platelet group (platelet $> 209\times10^9$/L, $n=57$). The multiple imputation statistical method did not impact the cutoff value for platelet count. The participants in the lower-platelet group displayed elevated white blood cell and reduced neutrophil levels in comparison to those in the higher-platelet group (Table 1). After survey weighting, 43.95% of the population ($n=121078$, CI 95% 43.76–44.13) were assigned to lower-platelet group with a mean PLT count of 174.93×10^9/L (SD 24.70), while 56.05% of the population ($n=154426$, CI 95% 55.87–56.24) were assigned to the higher-platelet group with a mean PLT count of 288.47×10^9/L (SD 61.15). No significant differences were identified with respect to the remaining demographic characteristics and hemodynamic indexes, including HbA1c, LDL, HDL, total cholesterol, triglyceride, red blood cell, lymphocyte, and hemoglobin between the two groups (Table 1). The mean time from PLT tested to stroke diagnosis was 10.93 years (95%CI 7.46–14.39) in the lower-platelet group and 9.95 years (95%CI 6.44–13.46) in the higher-platelet group. The mean time from PLT tested to cancer diagnosis was 9.65 years (95%CI 7.42–11.87) in the lower-platelet group and 13.02 years (95%CI 9.30–16.73) in the higher-platelet group. Between two groups, there were no significant differences in the time from PLT tested to stroke diagnosis ($P=0.45$) or PLT tested to cancer diagnosis ($P=0.70$).

The association between platelet level and all-cause mortality

The median survival time for all participants was 42 months (interquartile range (IQR), 23–74 months). There were 9 patients (7.96%) died of cerebrovascular diseases, 31 patients (27.43%) died of tumors, 32 patients died of heart diseases (28.32%) and 47 patients (41.49%) died of other diseases. In accordance with our criteria for survival status, 43 of the 113 (38.05%) participants were classified as survivors, as their survival time was greater than or equal to 60 months. A number of 70 participants (61.95%) met the criteria for classification as non-survivors, having exhibited a survival time of less than 60 months. The multivariate adjusted RCS regression model indicated a positive linear relationship between platelet count and all-cause mortality risk among stroke patients with cancer (nonlinear, $P=0.193$) (Fig. 2B). Survey-weighted Cox regression analysis demonstrated that platelet count was not statistically associated with all-cause mortality in crude model ($P=0.08$; Table 2). However, after the application of multivariate adjustments, a statistically significant association was observed between platelet count and all-cause mortality (Model 1, $P=0.01$; Model 2, $P=0.04$) (Table 2). The risk of all-cause mortality was found to be significantly elevated for patients with lower platelet levels compared to those with higher

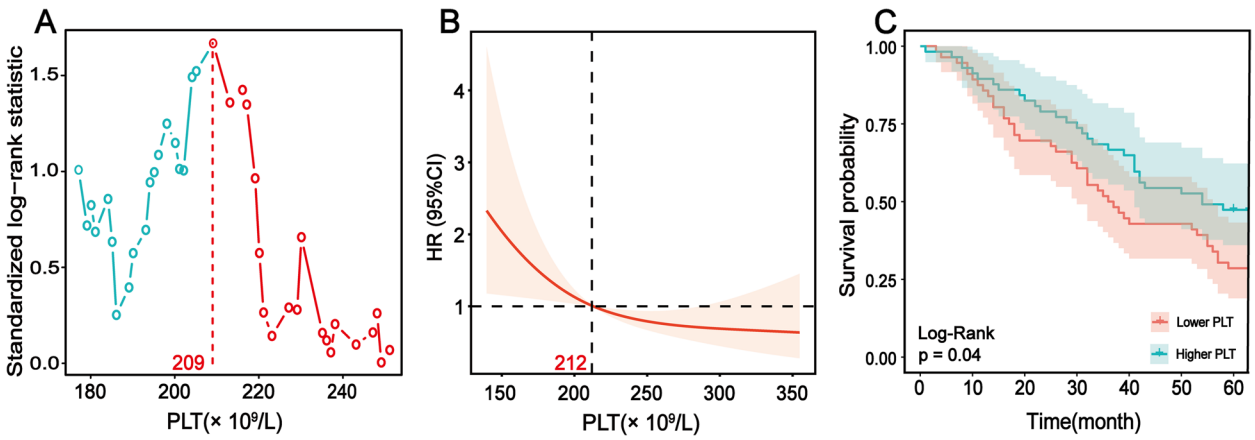

Fig. 2 Platelet level was associated with all-cause mortality in stroke patients with cancer. **A** Maximum selected rank statistics (MSRS) calculated an optimal platelet cut-off point of 209×10^9/L with a most significant association with survival rates. **B** Restricted cubic spline (RCS) curves suggested a positive linear relationship of PLT with survival. Hazard ratios controlled age, gender, race, family income-poverty ratio, educational level, alcohol history, smoke history, hypertension, diabetes, coronary heart disease, HbA1c, BMI, HDL, LDL, total cholesterol, triglyceride, white blood cell, red blood cell, lymphocyte, neutrophil and hemoglobin. *P* value for nonlinearity > 0.05. **C** Kaplan–Meier curves of survival rates showed the difference in all-cause mortality of stroke patients with cancer between higher-platelet and lower-platelet groups. PLT, platelet

Table 1 Baseline characteristics of participants with stroke and cancer based on multiple imputation, NHANES 2007 to 2018 (Unweighted)

Variable	Total($n=113$)	PLT $\leq 209\times10^9$/L ($n=56$)	PLT $>209\times10^9$/L ($n=57$)	*P* value
Gender,%				0.18
Male	61.06(51.40,69.96)	67.86(53.91,79.35)	54.39(40.75,67.43)	
Female	38.94(30.04,48.60)	32.14(20.65,46.09)	45.61(32.57,59.25)	
Age, y	72.25(72.67,75.83)	74.39(72.07,76.72)	74.11(71.89,76.32)	0.99
Race,%				0.42
Mexican American	1.77(0.31,6.88)	0	3.51(0.61,13.16)	
Non-Hispanic White	71.68(62.30,79.56)	69.64(55.74,80.84)	73.68(60.09,84.06)	
Non-Hispanic Black	20.35(13.60,29.18)	25.00(14.81,38.65)	15.79(7.91,28.37)	
Others	6.19(2.74,12.80)	5.36(1.39,15.80)	7.02(2.27,17.83)	
Education levels,%				0.53
Less than high school	41.59(32.51,51.25)	42.86(29.97,56.73)	40.35(27.84,54.16)	
High school or equivalent	22.12(15.08,31.10)	17.86(9.34,30.85)	26.32(15.94,39.91)	
College or above	36.28(27.60,45.91)	39.29(26.79,53.25)	33.33(21.75,47.17)	
Family income-poverty ratio,%	2.10(1.86,2.34)	1.99(1.65,2.32)	2.21(1.85,2.56)	0.36
Alcohol,%				1.00
Yes	76.99(67.94,84.16)	76.79(63.27,86.60)	77.19(63.84,86.84)	
No	23.01(15.84,32.06)	23.21(13.40,36.73)	22.81(13.16,36.16)	
Smoke,%				1.00
Yes	73.45(64.17,81.11)	73.21(59.46,83.77)	73.68(60.09,84.06)	
No	26.54(18.89,35.83)	26.79(16.23,40.54)	26.32(15.94,39.91)	
Hypertension,%				1.00
Yes	84.96(76.72,90.74)	85.71(73.22,93.20)	84.21(71.63,92.09)	
No	15.04(9.26,23.28)	14.29(6.80,26.78)	15.79(7.91,28.37)	
Diabetes,%				0.85
Yes	42.48(33.34,52.13)	41.07(28.37,54.99)	43.86(30.98,57.57)	
No	57.52(47.87,66.66)	58.93(45.01,71.63)	56.14(42.43,69.02)	
Coronary disease,%				0.25
Yes	20.35(13.59,29.18)	25.00(14.81,38.65)	15.79(7.90,28.37)	
No	79.65(70.82,86.40)	75.00(61.35,85.19)	84.21(71.63,92.09)	
HbAc1,%	6.13(5.90,6.36)	5.89(5.67,6.11)	6.36(5.99,6.77)	0.06
WBC, $\times10^9$/L	8.07(7.07,9.07)	8.10(6.20,10.00)	8.04(7.28,8.79)	0.02
RBC, $\times10^9$/L	4.37(4.24,4.51)	4.34(4.17,4.51)	4.41(4.21,4.61)	0.47
LY, $\times10^9$/L	2.34(1.54,3.15)	2.84(1.21,4.46)	1.86(1.63,2.09)	0.24
NE, $\times10^9$/L	4.76(4.39,5.14)	4.29(3.83,4.76)	5.23(4.65,5.80)	0.01
Hb, g/l	13.47,13.11,13.82)	13.48(12.92,14.04)	13.45(13.00,13.90)	0.88
TC, mmol/L	4.60(4.34,4.85)	4.47(4.14,4.81)	4.71(4.33,5.10)	0.48
TG, mmol/L	1.55(1.25,1.86)	1.42(1.21,1.63)	1.68(1.10,2.26)	0.40
LDL, mmol/L	2.59(2.40,2.79)	2.55(2.28,2.83)	2.64(2.35,2.92)	0.67
HDL, mmol/L	1.30(1.20,1.40)	1.26(1.12,1.40)	1.35(1.21,1.49)	0.36
BMI, kg/m^2	27.14(26.01,28.28)	27.16(25.35,28.97)	27.12(25.69,28.56)	0.97

Abbreviation: *HbA1c* glycosylated hemoglobin, *PLT* platelet, *WBC* white blood cell, *RBC* red blood cell, *LY* lymphocyte, *NE* neutrophil, *Hb* hemoglobin, *TC* total cholesterol, *TG* triglyceride, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *BMI* body mass index. Continues variables are presented as the mean and 95% confidence interval, category variables are described as the percentage and 95% confidence interval

platelet levels in both unadjusted (HR 0.61, 95% CI 0.38–0.98, $P=0.04$) and adjusted models (Model 1, HR 0.43, 95% CI 0.24–0.77, $P=0.005$) (Model 2, HR 0.58, 95% CI 0.35–0.96, $P=0.03$) (Table 2). The Kaplan–Meier survival rates combined with log rank test revealed significant discrepancies in the mortality curves between the lower- and the higher-platelet groups over the follow-up period (Fig. 2C). The five-year survival rate was significantly lower in the lower-platelet group than in the higher-platelet group.

Table 2 Relationship of platelet and all-cause mortality in stroke patients with cancer (Unweighted)

	Crude model HR(95% CI) P		Model 1 HR(95% CI) P		Model 2 HR(95% CI) P	
PLT	1.00(0.99,1)	0.08	0.99(0.99,1.00)	0.01	0.996(0.99,1.00)	0.04
PLT category						
Lower PLT	Ref		Ref		Ref	
Higher PLT	0.61(0.38,0.98)	0.04	0.43(0.24,0.77)	0.005	0.58(0.35,0.96)	0.03

Crude model was unadjusted. Model 1 controlled age, gender, race, family income-poverty ratio, educational level, alcohol history, smoke history, hypertension, diabetes, coronary heart disease, glycosylated hemoglobin, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglyceride, white blood cell, red blood cell, lymphocyte, neutrophil and hemoglobin. Model 2 was adjusted for age, gender, BMI, white blood cell and neutrophil

Abbreviation: *PLT* platelet

Table 3 Subgroup analysis of the association between platelet and all-cause mortality among stroke patients with cancer (Unweighted)

Characteristic	Low PLT (> 209×10^9/L)	High PLT HR (95%)	*p*	p for interaction
Overall	1	0.61(0.38,0.98)	0.04	
Age				0.10
< 60	1	0.17(0.02,1.51)	0.11	
≥ 60	1	0.69(0.42,1.14)	0.15	
Gender				0.81
Male	1	0.63(0.34,1.17)	0.14	
Female	1	0.56(0.27,1.18)	0.13	
BMI				0.15
< 18	1	3.46(0.22,55.78)	0.38	
18–24	1	0.72(0.32,1.64)	0.44	
> 24	1	0.58(0.31,1.07)	0.08	
WBC				0.51
< 10	1	0.56(0.33,0.94)	0.03	
≥ 10	1	0.92(0.28,3.04)	0.90	
NE				0.50
< 7		0.74(0.38,1.42)	0.36	
≥ 7		0.55(0.27,1.11)	0.10	

Abbreviation: *BMI* Body mass index, *WBC* white blood cell, *NE* neutrophil, *HR* hazard ratio. HR were adjusted for age, gender, BMI, WBC and NE

Subgroup analysis for interaction between selected variables and platelet

The interaction effects of platelet level and other variables on the risk of all-cause mortality were examined in detail through subgroup analyses stratified by sex, age, BMI, white blood cell and neutrophil (overall $P=0.04$, Table 3). These potential influencing factors were identified through a multivariate COX regression analysis. Certain factors that may impact patient survival, such as stroke therapy and anti-tumor treatment, were not included in this study due to their absence in the NHANES database. No significant interaction between the other aforementioned characteristics and the platelet levels was found in the present study (P for interaction > 0.05). However, in patients with a white blood cell count of $<10\times10^9$/L, the risk of all-cause mortality was found to be significantly lower in the higher-platelet group compared to the lower-platelet group ($P=0.03$).

The predictive ability of platelet level for all-cause mortality in stroke patients with cancer

Time-dependent ROC analysis was performed to evaluate the predictive value of platelet level for risk of all-cause mortality in stroke patients with cancer (Fig. 3A). The area under the curve (AUC) of platelet level was 0.54 (95%CI 34.76–74.10) at 1 year, 0.55 (95%CI 42.29–67.06) at 2 years, 0.57 (95%CI 45.61–67.62) at 3 years, 0.53 (95%CI 42.80–64.19) at 4 years, 0.59 (95%CI, 48.88–70.03) at 5 years (Fig. 3A and B). These findings indicated that platelet level have a potential predictive ability for risk of all-cause mortality in stroke patients with cancer across different time periods.

Discussion

This retrospective study demonstrated an independent association between platelet level and the risk of all-cause mortality in stroke patients with cancer. Compared with higher platelet level, platelet $\leq 209\times10^9$/L significantly elevated the risk of all-cause mortality by 32% ~ 57% in patients with a history and cancer. The remarkable effect of platelets on all-cause mortality in stroke patients with cancer was not influenced by age, gender, race, WBC count and other medical history.

Hematological disorders such as essential thrombocythemia and thrombotic thrombocytopenic purpura are frequently overlooked as potential causes of cerebrovascular diseases. In fact, 1.27% of first-ever ischemic strokes and 1.03% of first-ever hemorrhagic strokes can be attributed to hematological disorders [20]. Therefore, it is crucial to emphasize the need for laboratory examination and specific management strategies for this particular

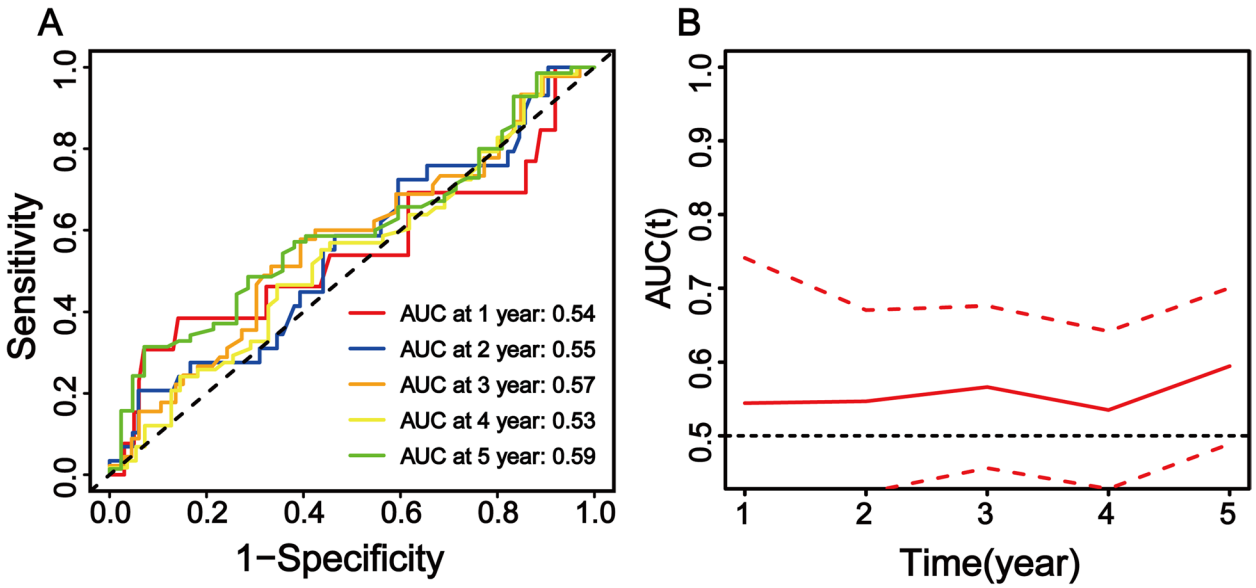

Fig. 3 Time-dependent ROC curves (**A**) and the area under the curve (AUCs) (**B**) demonstrated predictive value of platelet level for all-cause mortality

group of individuals. Disseminated intravascular coagulation caused by activated procoagulants has been considered to be the most important mechanism leading to multiple arterial thromboemboli in cancer patients. Extensive evidences from both experimental and clinical trials had demonstrated the close relationship between platelet and the incidence of thromboembolic events in tumor patients. Histopathological studies showed a platelet-rich features of thrombi in patients with stroke and active cancer [21, 22]. Thrombus extracted through endovascular thrombectomy in cancer patients exhibited higher platelet fractions and lower erythrocyte fractions. Carcinoma cells from mucinous adenocarcinomas frequently upregulated the expression of a variety of mucin polypeptides in the bloodstream [23]. These polypeptides acted as pathological ligands for the selectin family of adhesion molecules. Since carcinoma mucins and mucin fragments have binding sites for P-selectin and L-selectin on platelets, selectin-mucin interactions rapidly generated platelet-rich thrombi in small blood vessels and cause disseminated microangiopathy [23]. Clinical trials have demonstrated that patients with stroke and cancer typically present with elevated levels of D-dimer, C-reaction protein and P-selectin, while exhibiting decreased platelet counts relative to those without cancer [4, 10, 14]. These altered hematological factors mediated the incidence of recurrent stroke and the adverse prognosis in cancer patients. A retrospective analysis revealed that primary brain tumors increased the risk of venous thromboembolism by over-expressing podoplanin, a transmembrane glycoprotein. Podoplanin served as an effective agonist for platelet aggregation, leading to a notable reduction of platelet counts and D-dimer levels in circulation [24]. The substantial consumption of platelets in active cancer patients reflected a possible association between a higher risk of hypercoagulability and decreased platelet levels.

In addition, a few of studies discovered platelet reduction may be associated with poor prognosis in patients with cancer-related stroke. A population-based longitudinal cohort study was conducted to evaluate the association between platelet count and the incidence of cardiac and cerebral vascular disease, as well as mortality. Both participants with low (< 100, 100 to 199×10^9/L) and high (300 to 399, and above 400×10^9/L) platelet counts exhibited a higher incidence of non-cardiovascular mortality, including cancer [25]. In a clinical trial involving 1570 consecutive stroke patients, it was found that low platelet levels were predictive of a poor clinical outcome for individuals with cancer [4]. The patients with active cancer who exhibited a poor mRS score at discharge were found to have lower platelet levels [4]. The present study provided direct evidence that a lower-platelet level was an independent predictor of an elevated risk of all-cause mortality in stroke patients with cancer. This result was achieved by utilising adjusted models fitted by survey-weighted Cox regression analysis.

A growing of evidence have confirmed the predictive effect of higher D-dimer level on poor prognosis and mortality in stroke and tumor patients [7, 26, 27]. The

correlation between baseline platelet levels and prognosis of stroke with cancer has yet to be adequately addressed. In this study, the analysis of platelet count as a continuous variable did not show any statistically significant associations with all-cause mortality. Upon further investigation, we performed MSRS and determined an optimal platelet cut-off value of 209×10^9/L, which had the most significant impact on the survival status. Subsequently, we found the patients with a platelet count below cut-off point had an increased risk of all-cause mortality. The optimal threshold obtained by MSRS was highly comparable to the threshold obtained by the ROS curve, with a discrepancy of only 3. Moreover, by incorporating time-dependent settings in the sensitivity and specificity analysis of platelet-time data for mortality, we further determined the capability of platelets in predicting all-cause mortality during a 5-year follow-up period. The AUC values for 1 to 5 years of mortality were greater than 0.5 especially for 5 years (AUC = 0.57) but no more than 0.59. This funding suggested that in a cross-sectional analysis, the baseline platelets may have a low potential predictive ability for mortality in the population with cancer and stroke. Further high-quality clinical research is needed to confirm and expand upon our current findings, and to explore the potential implications of platelet levels for the development of targeted treatment strategies for stroke patients with cancer.

Cancer-associated stroke often presents as multiple lesions involving both the anterior and posterior circulation [28]. Previous studies have suggested that most infarcts in the posterior cerebral artery are lacunar and that patients tend to have a better prognosis than those with anterior circulation infarcts [29]. However, due to the absence of imaging data in the current study, the prognostic relationship between infarct location and mortality in patients with stroke and cancer remains uncertain.

Despite the AUC values not being near 1, our findings suggested that platelets may still have potential as a prognostic marker for stroke patients with cancer. It is important to consider several limitations of the present analysis. Despite combining 11 years of nationally representative NHANES data, the number of cases was relatively small due to the absence of essential data on platelet count (n = 147) and mortality in a portion of objectives. In order to achieve efficient fitting models, we selected a limited number of variables for analysis. Other factors, such as treatment methods (anti-thrombolysis or anticoagulant therapy) and whether to receive anti-tumor therapy, could affect the statistic results [30], resulting in a small predictive AUC value under ROC curve. Because the time interval between the laboratory test and stroke onset and the diagnosis of malignancy was not constant, the NHANES database primarily showed the platelet values in the stable stage of stroke. Consequently, the findings of this study could not be used to forecast the relationship between acute stroke platelet levels and all-cause mortality in stroke patients with cancer. The NHANES database questionnaire did not provide specific information regarding stroke types, temporality, and tumor staging. Consequently, platelet effects on all-cause mortality may manifest differently across subgroups in stroke patients with cancer, such as in cases of ischemic versus haemorrhagic stroke. Despite microthrombosis potentially consuming a significant number of platelets [22], it is undisputed that tumor cells frequently activate platelets by secreting a range of cytokines and procoagulant mediators. Therefore, the predictive survival model of lower platelet levels in stroke patients with cancer proposed in this study is not in contradiction with the application of antiplatelet and anticoagulant therapy in cancer patients.

Conclusions

Our study indicated a close association between the platelet level and the survival status of the population with a history of stroke and cancer, suggesting that the baseline platelet level may serve as a potential independent biomarker for predicting the risk of all-cause mortality in this population although with a low potential predictive ability. The lower platelet maybe associated with shorter survival in stroke patients with tumor. Identifying and monitoring platelet levels could potentially help healthcare professionals in predicting and managing the course of the disease for these individuals.

Abbreviations

NBTE	Non-bacterial thrombotic endocarditis
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
CNSR	China National Stroke Registry;
NHANES	National Health and Nutrition Examination Survey
CDC	United States Centers for Disease Control
NCHS	National Center for Health Statistics
NDI	National Death Index
MSRS	Maximum selected rank statistics
MEC	Mobile examination center
BMI	Body mass index
HDL	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglyceride
HbA1c	Glycosylated hemoglobin
WBC	White blood cell
RBC	Red blood cell
NE	Neutrophil
HR	Hazard ratio
IQR	Interquartile range
AUC	Area under the curve

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2: Figure. S1 The variables contain missing data and patterns of missing data.

Supplementary Material 3: Figure. S2 Missing data were imputed using multiple imputation with five imputed models. These five models of imputation can be seen in the graph, where red dots are imputations and blue dots are actuals.

Supplementary Material 4: Figure. S3 Participants' time from cancer diagnosis to time of platelet testing and time from stroke diagnosed time to platelet testing.

Supplementary Material 5: Figure. S4 Participants' time from stroke diagnosed to cancer diagnosed.

Supplementary Material 6.

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Authors' contributions
YP, methodology, data curation and analysis, writing-original draft. WO, PQ and ZY, data collection and analysis. YL, data curation, supervision. XZ, CZ and LC, conceptualization, project administration, writing-review & editing.

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Data availability
The data for our research is available on request.

Declarations

Ethics approval and consent to participate
The study was conducted according to the Declaration of Helsinki. All data in this research was approved by and the Ethics Review Board of the National Center for Health Statistics in the USA (Protocol #2005–06, Protocol #2011–17, and Protocol #2018–01). All participants were required to sign an informed consent form approved by the Ethics Review Board of the National Center for Health Statistics.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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