Effect of Platelet Count on Prognostic Value in Patients with Chronic Heart Failure

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Research article

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Abstract

Background: The prognostic value of platelet count in chronic heart failure (CHF) is not clearly established. The present study aimed to assesse the independent prognostic value of platelet count in patients with CHF.

Methods: From Januay 2016 to December 2019, 1162 patients with a discharge diagnosis of CHF were recorded in present study. The patients were divided into two groups according to the platelet count: low platelet count (LP, ≦140,000/μl) and high plate count (HP, >140,000/μl). The main outcomes were defined as all-cause death or cardiogenic rehospitalization within 3 years. Survival analysis and Cox proportional hazard models adjusted by an established risk score were performed.

Results: During 3 years follow-up, the overall main outcomes including all-cause death (*P*=0.0475) and composite endpoint events of all-cause death or cardiogenic rehospitalization (*P*=0.0053) were higher in LP group than in those with HP group. After adjusting for other covariables, including gender, age, et al., low platelet count was related to increased the risk of main outcomes during 3 years follow-up (all-cause death, HR:1.151, 95%CI: 1.082-1.670, *P*=0.040; composite endpoint events, HR: 1.313, 95%CI: 1.152-1.964, *P*=0.016).

Conclusions: Low platelet count was associated with risk for higher adverse outcome in patients with CHF.

Background

In recent years, although there have been progress in the treatment of chronic heart failure (CHF), it remains a major public-health issue with high associated risks of morbidity and mortality and substantial associated economic costs. CHF patients are often admission to the hospital with acute onset of symptoms. Although various mechanisms have been commented, the causes of the development of acute decompensation in patients with stable CHF are still illegible. As well as, a reliable, simple, inexpensive and rapid prognostic marker for CHF patients is obviously needed.

Although CHF is well known to be associated with a prethrombotic or hypercoagulable state, the pathophysiology of thromboembolism in CHF is multifactorial and complex. Indeed, abnormalities in hemorheological function has been confirmed in CHF, while elevated markers of platelet activity. Platelets are essential for maintaining the integrity of the vascular system and are the first line of defense against bleeding. Chronic platelet activation is associated with an increased risk of capillary thrombosis [1]. A recent study carried out by Satoshi et al. [2] showed that low blood platelet count was a risk factor of all-cause death and the composite endpoint events in patients with CHF. The mean platelet volume, which represents platelet activation, was associated with the risk of heart failure hospitalization in patients with CHF [3]. Recent study reported that prognostic value of mean platelet volume in cardiovascular pathology [4–7], including correlation between mean platelet volume and exacerbated heart failure [8]. Several previous researches have illustrated that pro-thrombotic state and blood platelet activation are related to

the severity of acute heart failure and the underlying risk of heart failure worsening in patients with CHF. At the same time, age-related decrease in blood platelet count has been reported among healthy people [9]. However, it is reported that patients with symptomatic CHF have bone marrow dysfunction regardless of age [10]. In addition, in patients diagnosed with heart failure with reduced left ventricular ejection fraction for the first time, lower blood platelet count was a risk factor for 1-year mortality [11]. However, the prognostic value of platelet count in CHF remains illegible.

We have therefore undertaken a study to evaluate the effect of platelet count on prognostic value in patients with CHF. We sought to define the relationship of blood platelet count and CHF-related adverse outcomes of all-cause death and cardiogenic rehospitalization in patients with CHF.

Methods

Patients

The study population consisted of 1162 consecutive patients with exacerbated heart failure diagnosed with CHF, admitted to the Beijing Chaoyang Hospital and Second Affiliated Hospital of Shantou University Medical College from January 2016 to December 2019. The diagnosis of CHF was adjudicated by 2 independent cardiologists according to the American College of Cardiology/American Heart Association guidelines [12] for CHF. In the case of patients admitted on more than once during the study period, the only data included in the analysis were those corresponding to the first admission. Patients with acute coronary syndromes, severe infection, cancer, liver and renal dysfunction (eGFR < 60 ml/min/1.73 m^2) were excluded (Fig. 1). The whole group was divided into 2 subgroups according to the basic platelet count: low platelet count group (LP, platelet count ≦ 140,000/μl) and high platelet count group (HP, platelet count > 140,000/μl).

The protocol was approved by the Institutional Ethics Committee at the Beijing Chaoyang Hospital and Second Affiliated Hospital of Shantou University Medical College (No. SUMC2020-009). Patients were not required to provide written consent to enter the clinical database,since this was part of the routine clinical operations in the CHF clinic

Data collection

Hematological and biochemical measurements made at the time of admission were analyzed. Baseline information was obtained on demographic variables, medical history, medication use (medication on discharge), the main clinical findings upon admission, risk factors and supplementary examinations (echocardiography, electrocardiography). The results were obtained from the patients' medical histories.

Study endpoints

Data for each patient were censored 3 years after admission, so that there was 3 years follow-up for each patient. The primary end point of the study is defined as time from the first occurrence of death from any cause. Second outcomes included rates of composite endpoint events of all-cause death, 3-year

cardiogenic readmission to the hospital for unstable angina, worsening heart failure, stroke or myocardial infarction occurring during any rehospitalization

Statistical analysis

Continuous data are expressed as mean ± SD. Comparison of Continuous variables between LP and HP group was performed using Student's t-tests and chisquared test or Fisher exact test, as appropriate for qualitative variables, either categorical or ordered. The unadjusted cumulative survival and incidence of the endpoint events (all-cause death and combined endpoint enevts of all-cause death or cardiogenic rehospitalization) for patients with low and high blood platelet count were compared using Kaplan-Meier survival analyses and statistical significance was tested using a log rank test. Hazard ratios were generated by a Cox regression analysis. We used a Cox proportional hazard model with backward elimination to estimate adjusted hazard ratios. The resulting regression coefficients were used to estimate relative risks (RR) and the corresponding 95% confidence intervals (CI). A P value of < 0.05 was considered statistically significant. Statistical analysis was performed with GraphPad Prism 7.0 and SPSS for Windows Version 17.0 (SPSS, Chicago, IL).

Results

Baseline characteristics

Of the 1162 patients, 566 (48.7%) patients with low platelet count and 596 (51.3%) patients with high platelet count and baseline characteristics are summarized in table 1.

In general (table 1), patients with low platelet count mostly were old (years, 78.69 ± 15.38 vs. 74.07 ± 10.89, *P*<0.01) and female subjects (44.2% vs. 36.5%, *P*<0.01) with a history of valvular disease (27.4% vs. 11.1%, *P*<0.01) and diabetes mellitus (26.9% vs. 16.6%, *P*<0.01). Ischemic heart disease was the slightly more common etiology of CHF with low platelet count (64.0% vs. 58.9%, *P*=0.072), and more common combine with atrial fibrillation (38.9% vs. 33.3%, *P*=0.047). Patients with low platelet count were also more likely to have a longer history of heart failure.

Patients with low platelet count had a slightly but significantly lower mean LVEF compared with patients with high platelet count (47.11 ± 15.47% vs. 49.41 ± 14.56%, P<0.009). NT-pro-BNP, hs-TnT, left atrial and left ventricular dimension were generally higher in patients with low platelet count. There was no difference in essential hypertension and medication use

Survival Analysis

During the 3-year follow-up, a total of 199 (17.1%) deaths occurred, and 590 (50.8%) patients died or readmitted to hospital because of worsening heart failure, unstable angina, myocardial infarction or stroke occurring during any hospitalization. The unadjusted 3-year end point of all-cause death was 107 (18.9%) for patients with low platelet count and 92 (15.4%) for those with high platelet count (figure 2A,

Log rank P=0.0475), and unadjusted combined 3-year end point of death and readmission was 309 (54.6 %) for patients with low platelet count and 281 (47．1%) for those with high platelet count (figure 2B, Log rank P=0.0053), respectively.

Predictors of end point events of all-Cause Death

On Cox Proportional hazard model for adverse outcomes of all-cause death univariate and multivariable analysis (table 2), after adjustment for demographic and clinical covariates of underlying prognostic impact，low platelet count of blood was associated with increase the relative risk of 3-year overall mortality (HR=1.151, 95%CI: 1.082-1.670, *P*=0.040). Furthermore, a similar result was obtained on high sensitive troponin T (hs-TnT) in Cox multivariable analysis for all-Cause Death (table 2), elevated serum hs-TnT was a dependent risk factor for 3-year all-cause death in CHF (HR=1.680, 95%CI: 1.485-1.953, *P*=0.029).

Predictors of end point events of all-cause death and cardiogenic readmission

In all-cause death and cardiogenic readmission，univariate Cox analysis demonstrated that heart rate, age, systolic/diastolic blood presure, history of CHF, LAD, platelet count of blood and hs-TnT were significant risk factors for the combined endpoint of all-cause death and cardiogenic readmission in CHF (Table 3). Nevertheless, after adjustment for other covariates of lurking prognostic impact，heart rate, systolic/diastolic blood presure and LAD were not associated with significant higher risk of 3-year composite endpoint of all-cause death and cardiogenic readmission (table 3).

In the Cox proportional hazards model (table 3), variables associated with an increased risk of 3-year composite endpoint of all-cause death and cardiogenic readmission included low platelet count of blood (HR: 1.313, 95%CI: 1.152-1.964, *P*= 0.016), hs-TnT (HR: 2.411, 95%CI: 1.433-4.056, *P*=0.003) and age (HR: 1.009, 95%CI: 1.001-1.016, *P*=0.021) (table 3).

Discussion

As far as we know, the present study demonstrated that the progressive prognostic value of blood platelet count in CHF for the first time. Our results showed low blood platelet count was a dependent risk factor for adverse outcomes of all-cause death and the combined endpoint events of all-cause death and cardiogenic rehospitalization in patients with CHF. These findings are consistent with data reported in patients with acute heart failure in other studies [2]. Moreover, we also present the first-ever analysis of adversed outcomes risk markers in patients with CHF and show that hs-TnT, age and history of CHF as independent predictors of all-cause death and cardiogenic rehospitalization in patients with CHF.

CHF and blood platelet count

Platelets are crucial for maintaining the integrity of the vascular system and are the first line of defense against bleeding. Blood platelet activation associated with impaired endogenous platelet suppression and endothelial dysfunction is part of the CHF cardiovascular phenotype and leads to the increased risk for thromboembolic complications [13]. Approximately 11–44% of CHF patients will develop thrombotic complications [14]. One of the reasons for this might be a response forms to oxidative stress, which has been proven to be related to the prognosis of cardiovascular diseases [15]. Oxidative stress is defined as the overproduction of reactive oxygen species relative to antioxidant defense and has been shown to play an key role in the pathophysiology of CHF. In addition, it was found that the increase in oxidative stress is related to the functional severity of CHF, with the highest levels being noticed in patients in functional class III and IV [16]. Recent studies have demonstrated that oxidative stress may play a contributing factor in the platelet activation and platelet dysfunction observed in patients with CHF [17–29]. Moreover, previous studies indicated that mean platelet volume [4] and platelet-to-lymphocyte ratio [20–22] are strong and independent prognostic factors in patients with acute heart failure and CHF. Furthermore, Satoshi et al. [2] found that low blood platelet count was linked to all-cause death and cardiogenic readmission to hospital in patients with acute heart failure. Although many predictors of death and hospitalization have been identified, the predictive value of blood platelet count in CHF remains not clear.

Outcomes and predictors of endpoint events

The survivals of CHF patients have been found to be influenced by a wide range of demographic, functional, clinical, therapeutic and neurohormonal variables [11, 23]. Consistent with previous studies, we found that a large number of patient factors were associated with adversed outcome of all-cause death and cardiogenic rehospitalization in univariate analyses, and these broadly reflected blood pressure, age, history of CHF, comorbidity and clinical profiles. On multivariate analysis of Cox proportional hazard models narrowed these to lower blood platelet count, advancing age, history of CHF and higher serum hs-TnT. Although advancing age is a risk marker for most adverse events, and history of CHF is unsurprising given that adversed outcome were cardiogenic disease and comorbidity in origin, the other risk markers were potentially anticipated. Indeed, there are no data linking blood platelet count to adverse events in patients with CHF. However, low blood platelet count has been associated with all-cause death and the combine adversed endpoint events in patients with acute heart failure [2].

Previous study showed that thrombocytopaenia was associated with 1 year death in patients with CHF with reduced left ventricular ejection fraction (< 40%) [11]. Another recent research revealed that higher blood platelet was a predictors of sepsis death in patients with CHF and reduced left ventricular ejection fraction [24]. A key finding of our study was demonstrated that lower blood platelet count is a dependent risk factor for all-cause death and cardiogenic rehospitalization in patients with CHF. In this study, the outcomes were observed during 3-year follow-up in patients with low platelet count and compared to those with high platelet count. The results of this study is likely agreed with earlier reports in finding that low platelet count increases the risk of all-cause death and readmission to the hospital among acute heart failure patients [2].

Although CHF is a chronic disease, patients often presence acute symptoms. The mechanisms responsible for the development of acute attacks and the associated adverse consequences remain unclear. Recent studies demonstrated that acute heart failure was promoted not only by cardiogenic issues but also by systemic pathological changes such as a inflammatory and oxidant state [25]. Blood platelet may reflect those systemic pathological changes and suggest the severity of heart failure acute onset in patient with CHF. Our study included patients with CHF with preserved and reduced left ventricular ejection fraction, and showed that low blood platelet count was associated with adverse prognosis in such patients.

Study limitations

Our study provides entirely novel insights regarding the predictors of adversed outcomes in people with CHF. However, it is important to acknowledge the limitations of our study that will need to be addressed by future research. First, our study had a relatively short-term follow-up. Second, we cannot comment on whether lower platelet count underpins the association of our identified risk markers with increased risk of worsern outcomts. Third, the observational nature of our study prevents us from reaching causal inferences about the identified associations of risk markers. Finally, other measured and unmeasured factors might have influential outcomes.

Conclusions

In brief, lower bood platelet count may occur with potential pathophysiological changes in CHF. Low bood platelet count was associated with destitute prognosis in patients with CHF. Platelet count is widely measured in clinical conditions and can be easily convenient for use as a risk marker in patients with CHF.

Declarations

Author contributions

Conception and design of the research: LYB, LZ; Acquisition of data and Analysis and interpretation of the data: JZY, XY; Statistical analysis: JZY, XY; Writing of the manuscript: JZY; Critical revision of the manuscript for intellectual content: LYB, LZ. All authors have read and approved the manuscript.

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Availability of data and materials

The data can be obtained from the corresponding author under reasonable request.

Ethics approval and consent to participate

The ethics approvals of the retrospective study were obtained from Institutional Ethics Committee at the Beijing Chaoyang Hospital and Second Affiliated Hospital of Shantou University Medical College. Reference number: No. SUMC2020-009. Patients were not required to provide written consent to enter the clinical database, since this was part of the routine clinical operations in the CHF clinic The data used in this study was anonymized before its use.

Consent to publish

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1, table 2 and table 3 are only available as a download in the Supplemental Files section.

Figures

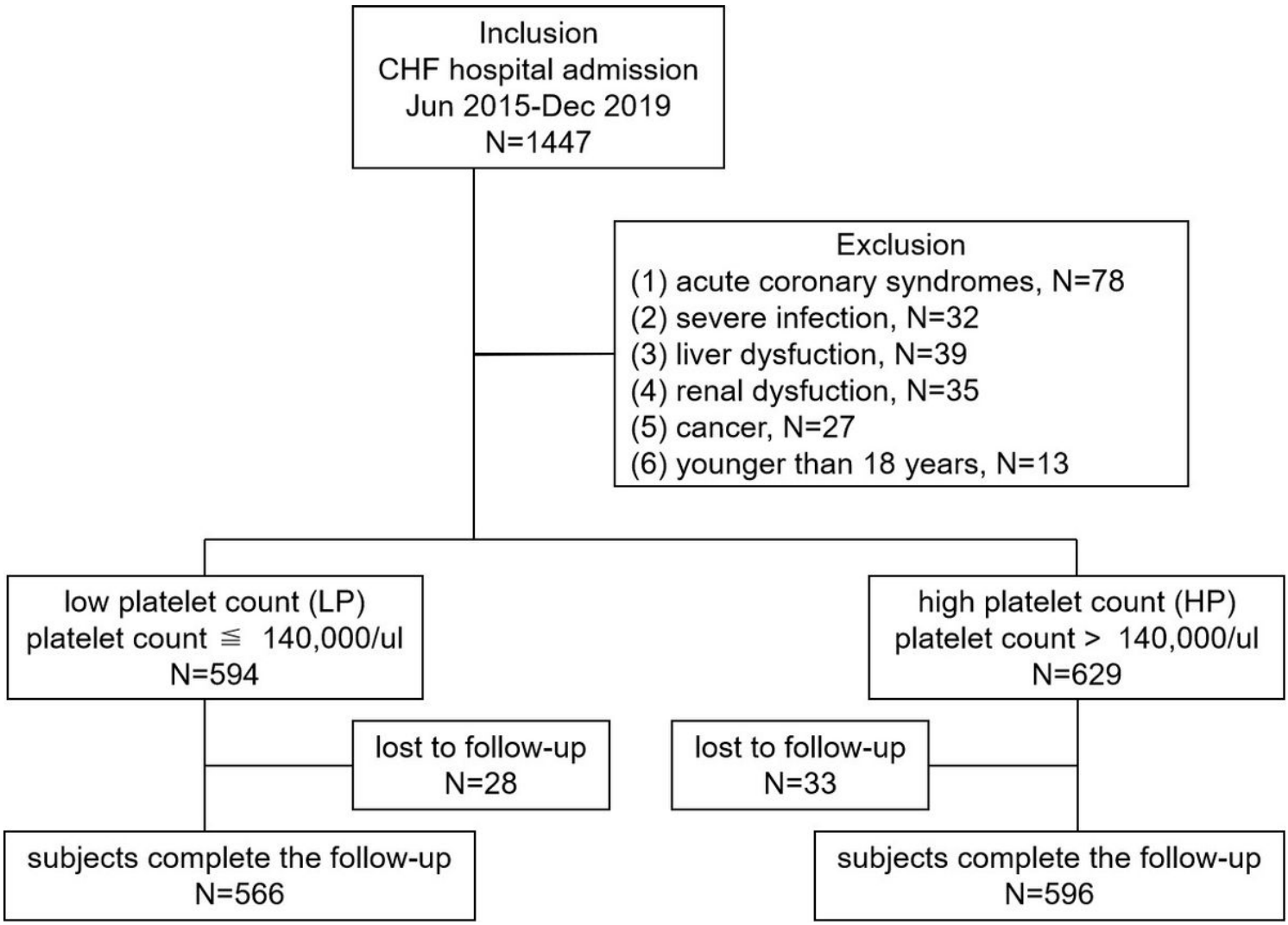

Figure 1

Flowchart of the patient with chronic heart failure (CHF).

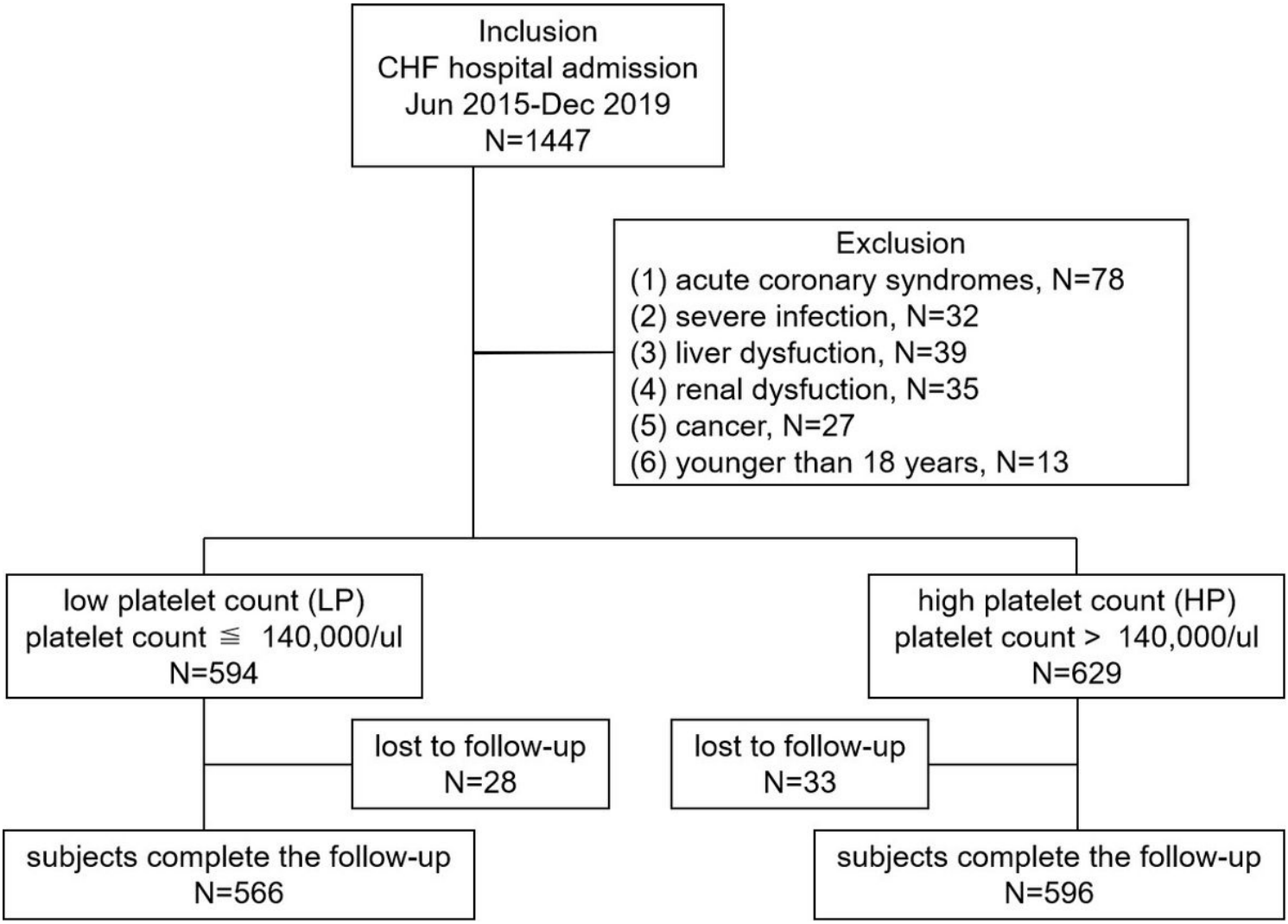

Figure 1

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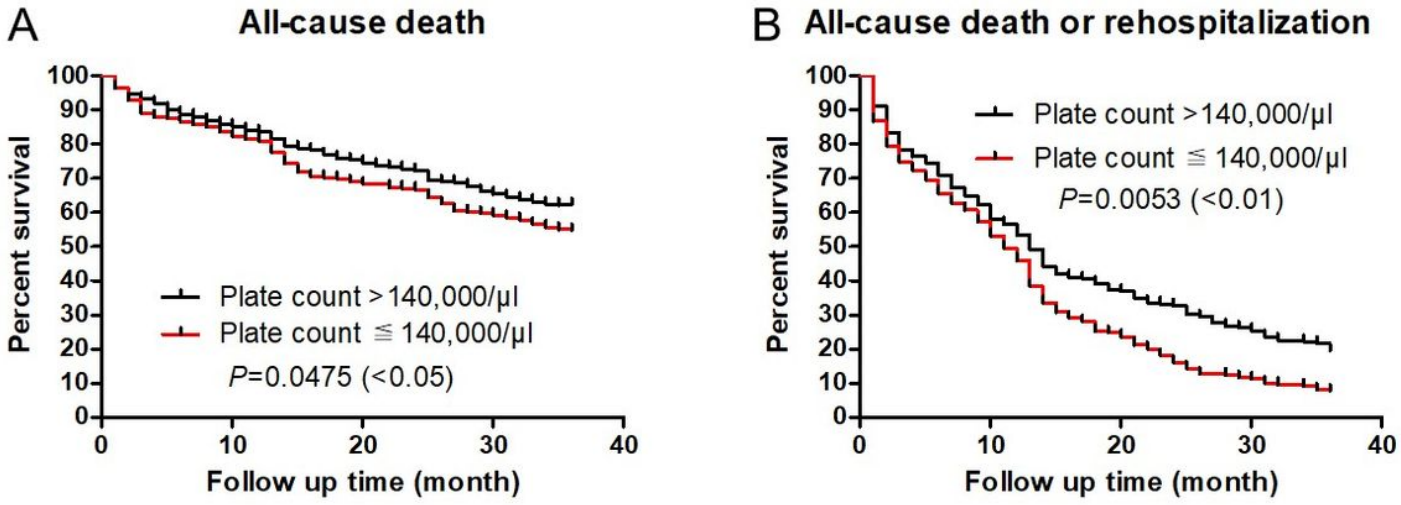

Figure 2

Kaplan-Meier probabilities of all-cause death (A) and composite endpoint events of all-cause death or rehospitalization (B).

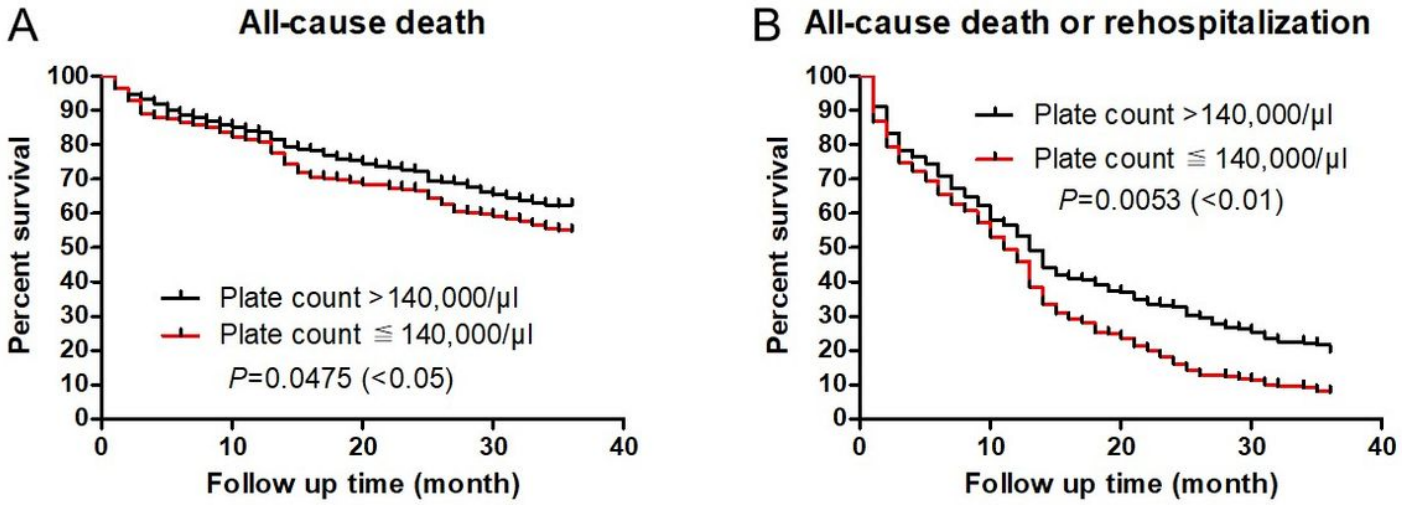

Figure 2

Kaplan-Meier probabilities of all-cause death (A) and composite endpoint events of all-cause death or rehospitalization (B).

Supplementary Files

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