Platelet count as risk indicator for cardiovascular events in hemodialysis patients

（血液透析患者における心血管イベント発症の

予測因子としての血小板数）

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Abstract

Background and aims: Patients receiving chronic hemodialysis (HD) are highly prone to develop cardiovascular events (CVE), and prognostic and preventive measures are of great value. Platelet count could be a simple prognostic indicator in the general population, but few pieces of research evaluated their significance in HD patients. This work aims to verify a prognostic value of platelet count in HD patients. I also sought to explore the pathophysiological background of such changes in platelet count.

Methods: I conducted a two-center retrospective cohort study of HD patients from 2008 to 2020. The primary endpoint was a composite of non-fatal myocardial infarction (MI), non-fatal stroke, and cardiovascular death. The Cox proportional hazard model evaluated the prognostic value of platelet count. I also explored other clinical backgrounds and laboratory data that could have affected platelet count or prognosis.

Results: Among 169 patients studied, 89 reached the endpoint within 12 years. By univariate and multivariate survival analyses, I confirmed that lower platelet count was an independent risk factor for future CVE. In the exploratory study, I found that lack of antiplatelet therapy (APT) was related to lower platelet count. The result suggested that hyperactivation and consumption were causes of mild thrombocytopenia. Surprisingly, the prescription of APT was paradoxically associated with worse outcomes among patients with lower platelet count. This result might

represent the insensitivity of the platelets to APT in such patients. I also found that platelet count correlated positively with white blood cells (WBC) and negatively with mean corpuscular volume (MCV), suggesting that the decrease of platelet count might also be associated with bone marrow dysfunction. Unexpectedly, patients who died of infection had lower platelet counts at the entry that was comparable to CVE cases, implying that alteration of immune systems may also account for lower platelet count.

Conclusion: Taken together, I conclude that platelet count can be a prognostic indicator of HD patients by representing some of the fundamental mechanisms underlying CVE.

Introduction

Patients receiving chronic hemodialysis (HD) are highly prone to develop cardiovascular events (CVE)[1]. Prognosis is even worse once they had encountered CVE[1]. Prevention is thus crucial, but not always as successful as in general populations. For instance, a high rate of severe bleeding compromises the value of antithrombotic agents to a considerable degree[2], and statins barely had the benefit on mortality from CVE[3]. Given that traditional risk factors failed to predict or prevent CVE sufficiently, it might be crucial to search for other risk indicators and therapeutic targets.

Alteration in the quality of platelets has gathered attention as a unique background of CVE[4]. Platelets from CVE patients are larger[5] and bear altered proteomes[6]. Faster turnover[7] and enhanced reactivity[8] in CVE patients might result in their insensitivity against antiplatelet therapy (APT)[9]. Among the reported changes in the platelets, the crude count is the most straightforward index related to cardiovascular outcome[10]. However, few studies evaluated these parameters for HD patients. Here, I sought to assess the prognostic value of platelet counts, and explore its pathophysiological backgrounds, in patients receiving chronic HD.

Patients and Methods.

The study had been reviewed and approved by The Ethics Committee at Chiba University

Graduate School of Medicine, and The Ethics Committee for Research of the Yamanouchi Hospital. I enrolled patients who received chronic HD in April 2008 at Chiba University Hospital or Yamanouchi Hospital, Japan, and conducted a retrospective cohort study in March 2020. Those with known causes that affect platelet counts (e.g., liver cirrhosis) or with a history of malignancy within five years from the enrolment date were excluded. I defined the primary endpoint as a composite of CVE, i.e., cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. I excluded non-CV death from the endpoint and identified them as being censored in the control arm. Medical records, health insurance records, and interviews provided clinical histories and events, as well as results of conventional blood tests.

Statistical analyses were performed by SPSS version 22.0 (IBM). All data were shown as average ± standard deviation unless otherwise noted. Two-tailed Student's t-test and Chi-square test served as univariate analyses. To determine the prognostic significance of each variable, I used Kaplan Meier Analyses and Log-rank tests. Pearson's test adjusted by partial correlation analysis evaluated associations among blood cell counts. To rule out potentially confounding factors, I utilized the Cox proportional hazard regression model as the primary multivariate analysis. Details in other statistical analyses were described in the manuscript or the figure legends. I considered analytical results significant when $p<0.05$.

Results.

Among 192 patients enrolled, 23 were excluded (3 with liver cirrhosis and 20 with malignancies), and the remaining 169 cases were studied. HD patients at 64.9 ±12.6 years of age were followed up for 63.9 ± 50.1 months (Table 1). Most patients had hypertension, and about 40% had diabetes mellitus, which were comparable to the average Japanese HD registry[11] and to the datasets from Taiwan or the United States, where the incidence of HD is the highest on the globe (United States Renal Data System. 2018 USRDS annual data report: https://www.usrds.org/2018/view/).

During the follow-up period, 89 patients (52.7%) reached the primary endpoint (Table 2). I found that higher age, larger mean corpuscular volume (MCV), and lower platelet counts were associated with CVE in univariate analyses. Smaller white blood cell (WBC) counts were weakly associated with the primary endpoint by P=0.052. Hyperlipidemia was associated with a lower incidence of CVE. This paradoxical result was irrespective of the use of statins, and we considered this as a type I error derived from fewer numbers of such patients. Other classical risk factors for atherosclerosis, nor some known factors that affect the prognosis of HD patients, were not significant in our patients. Kaplan Meier analyses and Log-rank tests, as well as Wilcoxon tests, showed that the patients with the platelet count in the lowest quartile showed significantly worse prognosis compared to other patients (Figure 1).

To investigate whether these factors were confounded, I conducted the Cox proportional hazard regression analysis (Table 3). I introduced the candidate variates from our univariate analyses and the variates that have a known clinical significance (platelet count, age, WBC, MCV, history of CVE, and prescription of APT or statin). I found that both the higher age and the lower platelet count remained independent and robust predictive factors that were associated with CVE. To verify that the history of CVE did not confound to the results, I conducted sub-analyses among primary (Table S1) or secondary (Table S2) prevention patients. Although the primary prevention group showed similar results to the overall picture, only the platelet count kept its significance in secondary prevention patients.

I then explored the remaining data to seek for any other potential backgrounds that could have affected the changes in the platelet count. First, I asked to investigate the impacts of medications. Prescriptions were available in 98 out of 169 patients in the cohort (Table 1). I found that those taking APT had significantly higher counts of platelet (Figure S1A). Although I could not detect the preventative value of the drug in our study samples (Table 3), it was striking that patients taking APT had worse prognosis when the platelet count was below the median (Figure S1B). Although there is a report that the prescription of statins decreases MCV[12], it did not correlate with MCV in our patients (data not shown). Erythropoietin, used in 92% of the cases, did not have an impact on prognosis, neither (Table 2).

I also compared platelet counts according to causes of death, i.e., cardiovascular, infection, and others (e.g., trauma, malignancies, and hypo-nutrition). Analysis of variance (one-way ANOVA) revealed that the distributions of platelet count were different depending on the causes of death. (Figure S2). Unexpectedly, I found that the patients who died from infection tended to have lower platelet counts at the entry, which seemed comparable to that of the CVE cases. These cases had lower WBC as well. Finally, I found that platelet count was correlated positively with WBC and negatively with MCV (Figure 2 A and B), which stayed significant after adjusting for the age of the patients (Figure 2C).

Discussion.

The prognostic value of platelet count has been controversial. While some studies showed that raise in the platelet count was associated with coronary heart disease in general populations[13], others found it negative[14]. The Caerphilly Prospective Study[10] showed a U-shaped relation of platelet count with stroke, where subjects with the lowest as well as with the highest platelet counts were prone to ischemic stroke. Here, I found that a reduction of the platelet count was predictive of future CVE in HD patients. To our knowledge, this is the first report that elucidated the prognostic value of platelet count in HD patients. In agreement with Ando et al., who showed that platelet count decreases chronologically in HD patients[15], I found that lower

platelet count was associated with age. Although higher age was strongly associated with CVE in our cohort (Tables 2, 3, and Figure 1B), lower platelet count also predicted adverse outcomes even after adjusting by age (Tables 3). Because HD patients undergo periodic blood tests in a usual clinical setting, it might be the easiest and the most practical way to discriminate cases that require screening or intensive follow up of cardiovascular diseases.

Pathophysiological backgrounds of the mild thrombocytopenia found in our retrospective patients remain unknown. However, our exploratory arm of the study showed a decrease in platelet counts among the cases without APT, suggesting that consumption of the platelet by its hyperactivation could be a cause. Accumulating evidence indicates that low-grade chronic inflammation is a risk of CVE in HD patients [16]. Oxidative stress, which is associated with chronic inflammation and malnutrition, may induce CVE[17] via endothelial dysfunction. Both of these mechanisms may induce prolonged activation and consumption of the platelet in vivo. Platelet-leukocyte aggregation, an established marker of platelet activation and hyperreactivity, may also play a part in the reduction of platelet count [18]. It is noteworthy that the cases with lower platelet count despite taking APT had the worst prognosis (Figure S1B). Such a paradoxical relation might indicate the insensitivity of the platelets to APT as a cause of CVE. Also, a substantial amount of platelets might be trapped by physical stress that they receive ex vivo during

the regular HD cycles[19]. The fact that the platelets from CVE cases already had impaired cytoskeletal proteome[6] should further support such a hypothesis.

Another potential mechanism for the platelet decrease could rely on alterations in hematopoiesis. Univariate analysis showed that larger MCV was associated with CVE, which was in line with a report showing that MCVpredicted adverse outcomes after coronary interventions[12]. A strong tendency toward decreased WBC was also evident in CVE cases. Moreover, the platelet count was significantly correlated with WBC and MCV, strongly suggesting that lower platelet count found in CVE cases may be representing bone marrow dysfunction and altered hematopoiesis[20].

I unexpectedly found that the platelet count and WBC in the patients who are going to die of infection were lower than other non-CVE deaths (Figure S2), which was comparable to the CVE cases. Reports show that the senescence of immune systems is found in HD patients [21]. It is noteworthy that in aged, hematopoietic stem cells tend to become platelet-primed[22] by epigenetic changes, which lead them to become prone to thrombosis[23]. Although I failed to accumulate any data in WBC fractions or platelet turnovers, it is highly suggested that lower platelet count found in these infection cases represented an altered state of immune systems, at least to some extent.

Taken together, mild thrombocytopenia found in the future CVE cases might be representing the following: impaired hematopoiesis, altered platelet quality, and compromised immune systems. All of these mechanisms are highly likely to be essential in the pathology of

CVE in HD patients. I believe that the hematopoiesis-platelet-CVE axis shall be a key and conventional target for investigations in HD patients.

Limitation.

There were several critical limitations to our study. First of all, because of its retrospective nature, I failed to obtain any measurements that could be a direct basis for our hypothetical discussions. However, results from our exploratory work may invite modern scientists to revisit these traditional indices in the era of high throughput molecular biology. Second, it was small in size and could not rule out any other potential confounders that reduced platelet counts. Nevertheless, the platelet count is readily available in any HD clinics, and being a prominent indicator of CVE, it may add prognostic value in daily clinical practices. And finally, due to the cross-sectional view of this study, I could not validate whether the hazard ratio regarding the lower platelet had been stable throughout the course, questioning the rationale to utilize the Cox hazard models. However, being confirmed by other statistical maneuvers, including the Log-rank test, Wilcoxon test, as well as Logistic regression models (Table S3), it is very likely that the results from these analyses were sufficiently reliable.

Conclusion.

In conclusion, I found that low platelet count is a risk indicator for CVE also in HD patients. Because platelet count is easily measurable, it would be of significant value for the prediction and prevention of CVE in HD patients. The relationship between the blood cell count and the emergence of CVE seems to imply the existence of an unknown mechanism in the development of CVE. The discoveries of the CVE risk indicator that is easily accessible in daily clinical practice and the presence of a possible unknown mechanism of CVE onset are essential contributions of this work.

Conflict of interest

There is no conflict of interest regarding this work to any of the authors.

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Figure legends

Table 1. The demographic background of the patients studied.

Distribution of demographic factors was equivalent to the average Japanese HD population, which is similar to that in the United States and Taiwan, where the incidence of HD is the highest in the world.

Table 2. Univariate analyses of demographic and laboratory indices.

Higher age, greater MCV, and lower platelet counts were significant indicators of the endpoint. Lower WBC was weakly associated with the primary endpoint.

Table 3. Cox proportional hazards regression analysis.

Candidate variates were selected from the results of the univariate analyses, and the variates that have a known clinical significance. Higher age and the lower platelet count remained independent and robust predictive factors that were associated with CVE.

Figure 1. Survival analyses

Patients with the platelet count in the lowest quartile (A), or the highest age quartile (B), showed significantly worse prognosis compared to other patients. Log-rank tests and Wilcoxon tests

confirmed their statistical significance.

Figure 2. Correlation of platelet count with WBC and MCV.

Platelet count correlated positively with WBC (A) and negatively with MCV (B), as confirmed by Pearson's test. Although these three indices were also associated with the age of the patients, the partial correlation analysis showed that these relations remained significant even after adjusting by age (C).

Table S1. Univariate analysis of the primary prevention arm.

Primary prevention group showed similar results to the overall picture.

Table S2. Univariate analysis of the secondary prevention arm.

Although the significance of age upon CVE was lost, the impact of platelet count remained in the secondary prevention arm, suggesting a pivotal role of platelet count in the prediction of CVE.

Table S3. Logistic regression analysis.

The logistic regression model was also applied to our data because I could not validate whether the platelet count had a hazard ratio that was proportional throughout the follow-up period, owing to the

cross-sectional nature of the current study. Nevertheless, platelet count and age remained significant, strongly suggesting that the results from the analyses were reliable.

Figure S1. Significance of APT on platelet count and prognosis

Patients taking APT had significantly higher counts of platelets (A). Interestingly, I found that patients taking APT had a paradoxically worse prognosis when the platelet count was lower than the median (17.6×10^4).

Figure S2. Platelet count and causes of death

Deceased patients in the cohort are divided into three groups based on causes of death. In the sub-analysis, the distributions of platelet count and WBC in each group are compared. Using one-way ANOVA it was shown that the distributions of platelet count was different depending on causes of death. In particular, platelet count were significantly lower in patients who died of infection or CVE than in patients who died of other causes. Similar trend was observed in WBC, though it was not statistically significant.

Table. 1

Follow up (Mo)	63.9 ± 50.1
Age	64.9 ± 12.6
Gender (Male)	105 (62.0%)
Diabetes	70 (41.0%)
Hypertension	155 (92.0%)
Hyperlipidemia	43 (25.0%)
History of CVE	53 (31.0%)
History of MI	10 (6.0%)
History of Stroke	45 (27.0%)
Prescription available	98 (58.0%)
APT prescribed	52 (53.0%)
Statin prescribed	16 (16.0%)
Injection note available	151 (89.3%)
Erythropoietin	139 (92.1%)

Table. 2

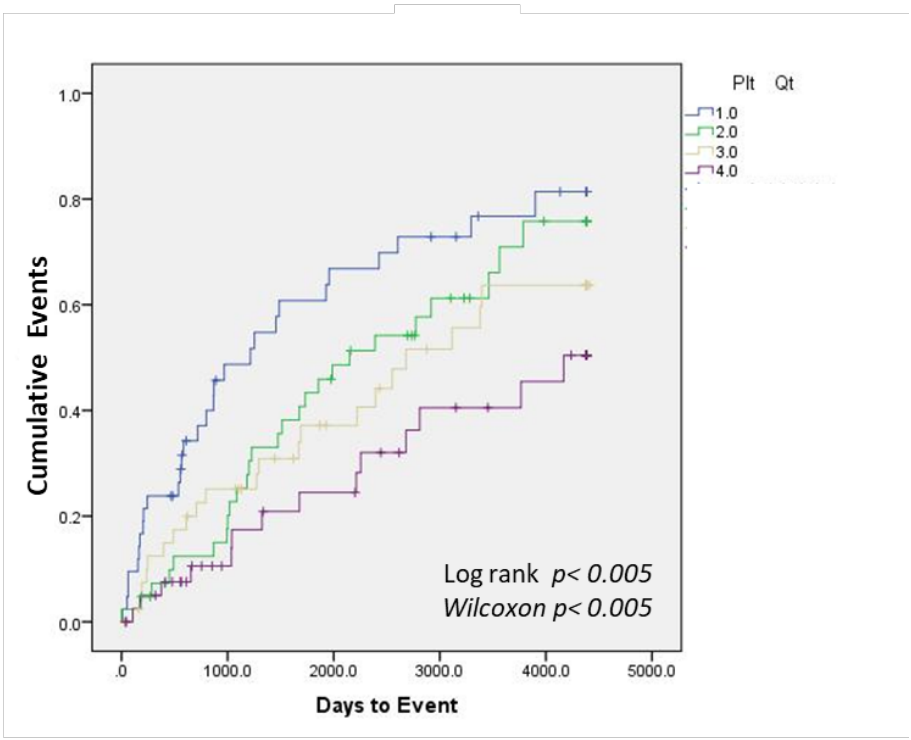
	Event (-) N=80	Event (+) N=89	*p*=
Age **	60.8 ± 13.2	68.6 ± 10.9	0.000
Gender	45 (56.3%)	60 (67.4%)	0.154
DM	32 (40.0%)	38 (42.7%)	0.756
HL *	27 (33.8%)	16 (18.0%)	0.022
HT	73 (91.3%)	82 (92.1%)	1.000
History of CVE	22 (27.5%)	31 (34.8%)	0.305
APT prescrition	30 (53.6%)	22 (52.4%)	0.907
Statin prescrition	10 (17.9%)	6 (10.7%)	0.784
Epo	67 (91.8%)	72 (92.3%)	0.784
WBC (*)	60.2 ± 22.6	54.1 ± 17.2	0.052
HGB	10.2 ± 1.1	10.1 ± 1.3	0.741
HCT	32.3 ± 3.3	31.8 ± 3.6	0.386
MCV *	93.3 ± 7.6	95.6 ± 6.9	0.049
PLT **	20.3 ± 6.9	16.4 ± 5.6	0.000
P	3.8 ± 0.4	3.7 ± 0.3	0.217
Alb	5.4 ± 1.6	5.3 ± 1.4	0.665
Ca	9.2 ± 1.0	9.1 ± 1.1	0.752
Ca x P	49.7 ± 16.5	48.4 ± 14.8	0.586

Table. 3

	B	SE	Wald	df	*p*=	Exp(B)	Exp(B) 95.0%
Age **	0.087	0.019	21.301	1	0.000	1.091	(1.051 - 1.132)
WBC	0.014	0.011	1.701	1	0.192	1.014	(0.993 - 1.035)
MCV	-0.027	0.023	1.287	1	0.257	0.974	(0.93 - 1.020)
PLT *	-0.082	0.037	4.932	1	0.026	0.921	(0.856 - 0.990)
History of CVE	-0.325	0.341	0.905	1	0.341	0.723	(0.37 - 1.411)
APT	-0.007	0.328	0.001	1	0.982	0.993	(0.522 - 1.887)
Statin	-0.187	0.459	0.166	1	0.683	0.829	(0.337 - 2.038)

Figure. 1

(A)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Cumulative Events
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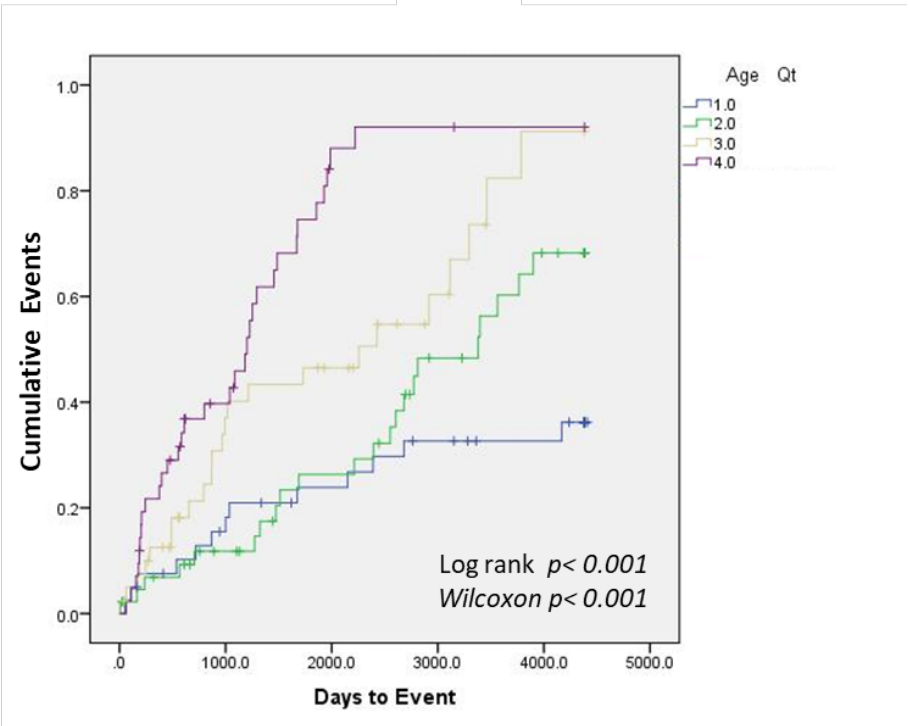
Days to Event
Log rank p< 0.005
Wilcoxon p< 0.005

(B)


Age Qt
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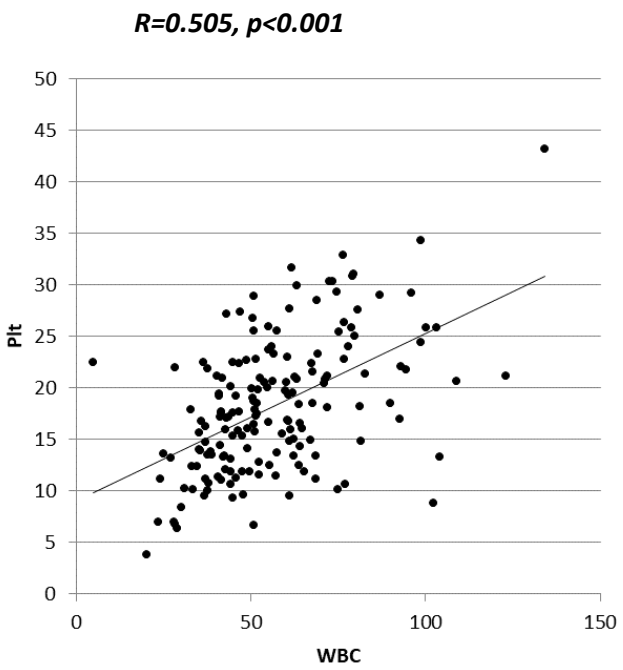
Days to Event
Log rank p< 0.001
Wilcoxon p< 0.001

Figure. 2

(A)



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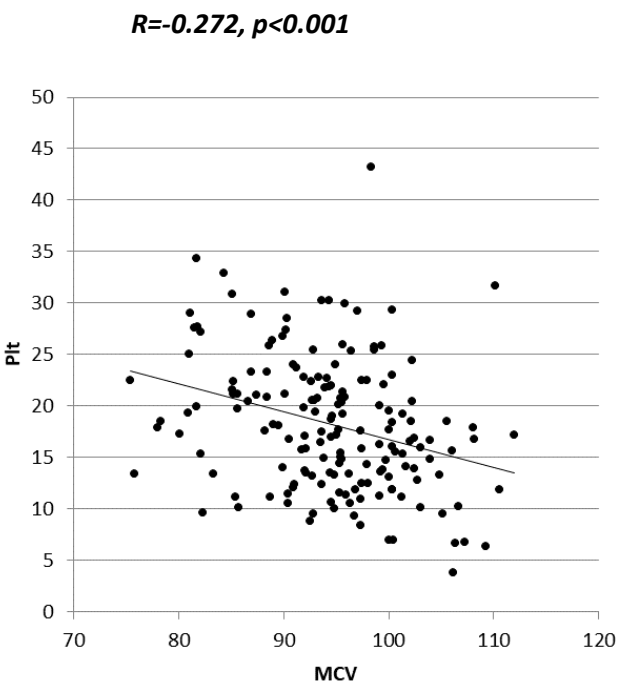


(C)

Control variables			WBC	MCV	PLT
Age	WBC	Correlation	1.000	-0.114	0.505
		Significance	.	0.140	0.000
		df	0	166	166
	MCV	Correlation	-0.114	1.000	-0.272
		Significance	0.140	.	0.000
		df	166	0	166
	PLT	Correlation	0.505	-0.272	1.000
		Significance	0.000	0.000	.
		df	166	166	0

Table. S1

	Event (-) N=58	Event (+) N=58	*p*=
Age **	58.5 ± 13.5	67.9 ± 10.8	0.000
Gender	33 (56.9%)	43 (74.1%)	0.078
DM	22 (37.9%)	21 (36.2%)	0.848
HL *	18 (31.0%)	9 (15.5%)	0.048
HT	53 (91.4%)	55 (94.8%)	0.464
History of CVE	0 (0.0%)	0 (0.0%)	-
APT prescrition	20 (46.5%)	13 (48.1%)	0.894
Statin prescrition	6 (14.0%)	5 (18.5%)	0.609
Epo	49 (92.5%)	46 (92.0%)	0.932
WBC	59.4 ± 24.2	54.2 ± 17.0	0.182
HGB	10.2 ± 1.1	10.2 ± 1.4	0.970
HCT	32.1 ± 3.2	31.9 ± 3.9	0.830
MCV	93.8 ± 7.5	95.5 ± 6.9	0.214
PLT **	20.8 ± 6.9	16.9 ± 5.7	0.001
P	3.8 ± 0.5	3.7 ± 0.3	0.390
Alb	5.5 ± 1.7	5.4 ± 1.5	0.841
Ca	9.2 ± 1.0	9.1 ± 1.1	0.658
Ca x P	50.9 ± 17.7	49.6 ± 15.0	0.671

Table. S2

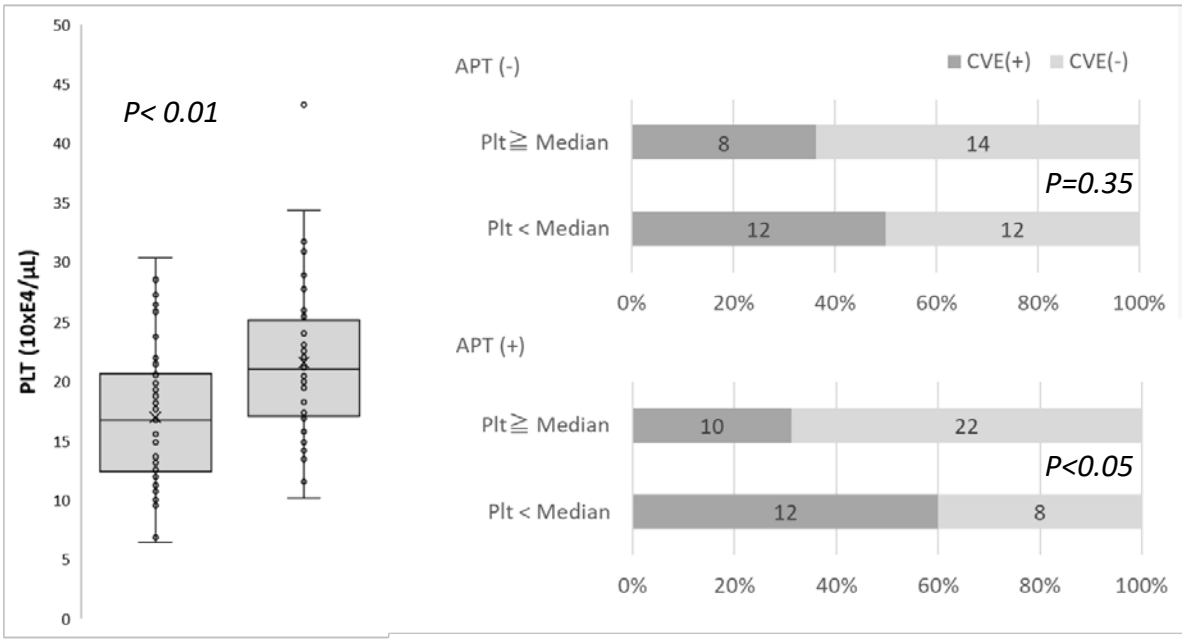
	Event (-) N=22	Event (+) N=31	*p*=
Age	66.9 ± 10.1	70.1 ± 11.2	0.289
Gender	12 (54.5%)	17 (54.8%)	0.983
DM	10 (45.5%)	17 (54.8%)	0.501
HL	9 (40.9%)	7 (22.6%)	0.152
HT	20 (90.9%)	27 (87.1%)	0.666
History of CVE	22 (100%)	31 (100%)	-
APT prescrition	10 (76.9%)	9 (60.0%)	0.339
Statin prescrition	4 (30.8%)	1 (6.7%)	0.097
Epo	18 (90.0%)	26 (92.9%)	0.724
WBC (*)	62.2 ± 18.2	53.8 ± 17.8	0.102
HGB	10.3 ± 1.1	10.1 ± 1.1	0.463
HCT	32.9 ± 3.6	31.7 ± 3.2	0.194
MCV (*)	92.2 ± 7.6	95.8 ± 7.2	0.089
PLT *	19.0 ± 6.8	15.5 ± 5.5	0.041
P	3.7 ± 0.3	3.6 ± 0.2	0.377
Alb	5.1 ± 1.2	5.0 ± 1.2	0.803
Ca	9.2 ± 1.0	9.2 ± 1.2	0.945
Ca x P	46.6 ± 12.7	46.2 ± 14.2	0.911

Table. S3

	B	SE	Wald	df	*p*=	Exp(B)	Exp(B) 95.0%
Age **	0.067	0.023	8.317	1	0.004	1.069	(1.022 - 1.118)
WBC	0.011	0.013	0.64	1	0.424	1.011	(0.985 - 1.037)
MCV	-0.001	0.034	0	1	0.984	0.999	(0.936 - 1.067)
PLT **	-0.137	0.049	7.724	1	0.005	0.872	(0.792 - 0.96)
History of CVE	-0.118	0.534	0.048	1	0.826	0.889	(0.312 - 2.533)
APT	-0.388	0.51	0.579	1	0.447	0.678	(0.25 - 1.843)
Statin	-0.004	0.662	0	1	0.995	0.996	(0.272 - 3.646)

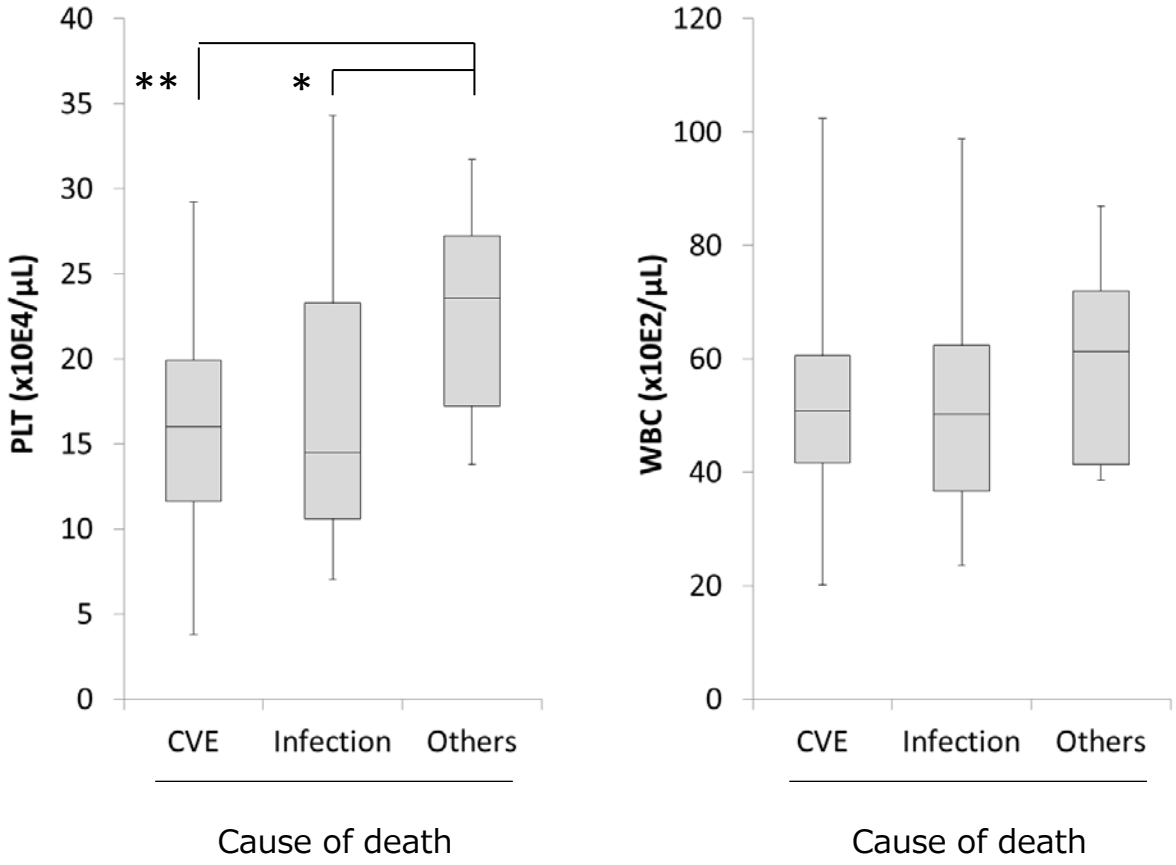
Figure. S1

A **B**



APT(-) APT(+)

Figure. S2


40
35
30
25
20
15
10
5
0
**
*
PLT (x10E4/μL)
CVE
Infection
Others
Cause of death
120
100
80
60
40
20
0
WBC (x10E2/μL)
CVE
Infection
Others
Cause of death