**Original article (Clinical investigation)**

# The effectiveness and safety of oral direct factor Xa inhibitors for the treatment of venous thromboembolism in patients with cancer and/or high age

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**Abstract**

Background: Venous thromboembolism (VTE) is a multifactorial disease, and cancer and high age are the risk factors for recurrent VTE, as well as bleeding on anticoagulant therapy. The oral direct factor Xa inhibitors (Xa inhibitors) have been widely used to treat VTE. However, their effectiveness and safety in cancer and elderly patients have not been fully elucidated.

Methods: A total of 187 consecutive patients who started Xa inhibitors for VTE therapy between September 2014 and September 2016 were recruited. Patients' demographics, changes in VTE amount, VTE recurrence, clinically relevant bleeding, and death until February 2017 were compared between 92 cancer and 95 non-cancer patients, and/or 57 elderly (≥ 75 years) vs. 130 non-elderly patients.

Results: Compared with non-cancer patients, cancer patients had a significantly higher incidence of deep vein thrombosis (DVT) in the proximal legs, superior vena cava, and upper extremities, but patients' demographics and proportion of pulmonary thromboembolism (PE) were similar in the two groups. There were no significant differences in VTE recurrence and clinically relevant bleeding between the two groups. Death occurred in 29 cancer patients, 23 of whom died of cancer, while none of the non-cancer patients died.

Elderly patients had a lower body weight and creatinine clearance than non-elderly

patients. No significant differences between the two groups were found in proportion with PE, DVT site, recurrent VTE, clinically relevant bleeding, and death.

In comparisons among the 4 groups (elderly or non-elderly patients with or without cancer), recurrent VTE and clinically relevant bleeding were comparable, and death was more frequent in cancer patients regardless of age.

Conclusion: The effectiveness and safety of Xa inhibitors as VTE treatment were comparable between cancer and non-cancer patients, and/or elderly and non-elderly patients. This suggests that Xa inhibitors may be promising drugs for VTE treatment, irrespective of age and comorbid cancer.

**Key words**: venous thromboembolism, oral direct factor Xa inhibitors, cancer, elderly.

## Introduction

Venous thromboembolism (VTE), which consists of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major healthcare problem resulting in significant morbidity and mortality. In particular, PE is recognized as the third most common cause of death from cardiovascular disease after heart attack and stroke in the United States (US).[1] In Japan, Nakamura et al. showed that the number of PE cases has increased 4.6-fold in the past 15 years, with the annual incidence estimated to be 126 per 1,000,000 people in 2011.[2]

VTE is a multifactorial disease, and it develops by genetic interaction with various environmental factors. Among the environmental risk factors, some are provoking (e.g. cancer, surgery, trauma or fracture, immobilization, pregnancy and the postpartum period, long-distance travel, hospitalization, catheterization, and acute infection) and others are non-provoking (e.g. age, sex, race/ethnicity, body mass index and obesity, oral contraceptive or hormone therapy use, corticosteroid use, diet, physical activity, sedentary time, and air pollution).[3] Indeed, cancer patients are known to have a 4 to 7-times higher risk of developing VTE.[4, 5] The Japan VTE Treatment Registry (JAVA) Study also showed that a history of cancer is the most common risk factor for VTE, present in 27.0% of VTE patients.[6] Therefore, cancer is a major cause of VTE.

Elderly persons are more affected by VTE than younger persons and have a higher proportion of severe and fatal VTE. The global annual incidence of symptomatic VTE was 1.83 per 1000 patients, but reached 10 per 1000 patients aged 75 years or older in France.[7] A post hoc analysis of the MEDENOX study showed that age ≥ 75 years was an independent risk factor for VTE.[8] Therefore, with increasing life expectancy, the increase in elderly people also leads to an increase in the number of VTE patients. On the other hand, patients having these risk factors, cancer and high age, also have a bleeding risk on VTE treatment with anticoagulants.[9, 10]

As the anticoagulants for VTE therapy, vitamin K antagonists (VKAs), unfractionated heparin, low-molecular-weight heparin, and factor Xa inhibitors are available. Anticoagulation using VKAs may become easily labile, because of drug interactions, malnutrition, and liver dysfunction, which indicates that VKAs are clinically inconvenient. The oral direct factor Xa inhibitors (Xa inhibitors) do not require laboratory monitoring or dose adjustment. Therefore, Xa inhibitors may be clinically attractive drugs for the treatment of VTE. Recently, the results of trials using Xa inhibitors for VTE therapy demonstrated that Xa inhibitors were non-inferior and safer than the standard heparin/VKA regimen.[11-14] However, their efficacy and safety in cancer and/or elderly patients have not been fully elucidated. Currently, 3 Xa

inhibitors, edoxaban, rivaroxaban, and apixaban, can be used for VTE therapy in Japan. The aim of this study was to examine the differences in the efficacy and safety of Xa inhibitors between cancer vs. non-cancer patients, and/or elderly vs. non-elderly patients.

## Materials and Methods

Patients' charts were reviewed retrospectively, and 187 consecutive patients who either started VTE treatment with Xa inhibitors, edoxaban (Lixiana ®, Daiichi-Sankyo, Tokyo, Japan), rivaroxaban (Xarelto ®, Bayer, Leverkusen, Germany), and apixaban (Eliquis ®, Bristol-Myers Squibb/Pfizer, New York, NY, USA), or were switched from other oral anticoagulants to Xa inhibitors for the treatment of VTE between September 2014 and September 2016 at Nagasaki University Hospital were recruited. VTE was confirmed by ultrasonography of the lower extremities, contrast-enhanced computed tomography, or magnetic resonance imaging. The classification of VTE and the DVT site were reported previously.[15] Briefly, VTE was classified as DVT only and PE with and without DVT, and the site of DVT was classified as proximal (between the inferior vena cava and knee joint), distal (below the knee joint), and upper (between the superior vena cava and upper extremities) DVT. Hematological data from within 1

week before starting the administration of Xa inhibitors was evaluated.

The approved doses of Xa inhibitors for the treatment of VTE in Japan are follows: the dose of edoxaban is 30 mg or 60 mg daily, depending on weight, renal function, and concomitant medications; the dose of rivaroxaban dose is 15 mg twice daily for 3 weeks followed by 20 mg once daily; and the dose of apixaban dose is 10 mg twice daily for a week followed by 5 mg twice daily.

The definitions of recurrence of VTE and clinically relevant bleeding were reported previously.[15] The occurrence of death was examined from the initiation of drug administration to February 28, 2017. When the status of survival or death was unknown, as in patients who transferred to other hospitals, they were defined as “uncertain”. Changes in the amount of thrombosis were examined in 148 patients who underwent at least two imaging tests, such as ultrasonography of the lower extremities and contrast-enhanced computed tomography, before and after administration of Xa inhibitors. The classification of changes in the amount of thrombus was based on the judgement of radiologists, sonographers, and cardiologists, as follows: normalized (no thrombus in the legs and lungs); improved (improvements in both the legs and lungs, or improvement in either the legs or lungs without deterioration at the other site); unchanged (unchanged results for both legs and lungs); and deteriorated (any

deterioration in either legs or lungs)[16]. When the patients underwent more than two imaging tests after starting Xa inhibitors, the earliest test in which changes in VTE became stable was adopted as the post-treatment test.[15]

In the present study, the effects of Xa inhibitors for VTE treatment on VTE recurrence, clinically relevant bleeding, and death were examined in patients with and without cancer (92 cancer and 95 non-cancer patients) and in elderly (≥ 75 years, 57 patients) and non-elderly patients (< 75 years, 130 patients).

This study complied with the Declaration of Helsinki with regard to investigations in humans, and the Ethics Committee of Nagasaki University Hospital approved the protocol. Because this was a retrospective study, an opt-out consent method was used instead of directly obtaining informed consent from the patients.

*Statistical analysis*

Continuous variables are expressed as means ± standard deviation for normally distributed variables, and as medians (interquartile range) for skewed variables; these variables were compared using the unpaired *t*-test and the Mann-Whitney U-test, respectively. Categorical variables are presented as absolute numbers and/or percentages and were compared using the chi-squared test. Kaplan-Meier analysis was used to estimate the cumulative incidence of events, and the log-rank test was used to

compare survival between the groups. Patients who developed VTE recurrence, clinically relevant bleeding, died, or stopped drug administration were censored. The significance level was set at $P < 0.05$. Statistical analysis was performed using EZR software version 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[17]

## Results

### *All patients*

For all patients, the median age was 67 years, females were predominant (62.0%), and average body weight was less than 60 kg (57.9±13.5 kg). The proportions of Xa inhibitors were 85% for edoxaban, 11% for rivaroxaban, and 4% for apixaban, and the median administration duration was 70.0 days.

### *Non-cancer vs. cancer patients*

The characteristics of patients with and without cancer are shown in Table 1. There were no significant differences between the two groups. The primary cancer lesion was mostly in the uterus and ovary (n = 26, 28.3%), followed by the gastrointestinal tract (n = 18, 19.6%), hepatobiliary and pancreatic organs (n = 10, 10.9%), brain (n = 8, 8.7%), blood (n = 8, 8.7%), and kidney and bladder (n = 6, 6.5%). Histopathological findings

indicated that most cancers were adenocarcinomas (n = 36, 39.6%), followed by squamous cell carcinomas (n = 17, 18.7%), malignant lymphomas (n = 7, 7.7%), and glioblastomas (n = 6, 6.6%).

The prevalence of DVT and PE were comparable between the two groups (Fig. 1A). Cancer patients had more DVT at the proximal and upper sites (p = 0.034, Fig. 1B). In terms of changes in the amount of thrombus, 87.3% and 82.6% of non-cancer and cancer patients, respectively, showed normalization or improvement in the thrombus, with no significant differences between the two groups (p = 0.526, Fig. 1C). The interval of the two imaging tests did not differ significantly [72.0 (14 -160) days in non-cancer patients vs. 61.5 (20.5-144.3) days in cancer patients, p = 0.327].

One non-cancer patient and two cancer patients developed recurrent VTE. The incidence was 1.1% and 2.1%, respectively, and no significant difference was found between the two groups (p = 0.328, Fig. 2A). Clinically relevant bleeding occurred in 3 non-cancer (3.2%) and 9 cancer patients (9.5%), but there was no significant difference between the two groups (p = 0.078, Fig. 2B). Among them, gastrointestinal bleeding occurred in 2 and 3 patients and cerebral bleeding occurred in 1 and 2 patients in the non-cancer and cancer groups, respectively. During observation, death occurred in 29 cancer patients (23 patients died from cancer). Therefore, the mortality rate was

significantly higher in cancer than in non-cancer patients ($p < 0.001$, Fig. 2C). Twenty-four non-cancer and 10 cancer patients were classified as “uncertain” patients, because these patients could not be followed.

***Non-elderly vs. elderly patients***

Elderly patients had significantly lower body weight and creatinine clearance than non-elderly patients. The D-dimer levels did not differ significantly between non-elderly and elderly patients (4.5 vs. 5.7 μg/ml, $p = 0.260$). The duration of Xa inhibitor therapy was not significantly different between the two groups. The proportion of cancer was significantly higher in non-elderly patients (56.2% in the non-elderly vs. 38.6% in the elderly, $p = 0.038$).

The proportion of PE did not differ significantly between the elderly and non-elderly patients (Fig. 3A), while DVT at the distal site tended to be more frequent in the elderly patients ($p = 0.054$, Fig. 3B). There were no significant differences in the change of the amount of thrombus ($p = 0.212$, Fig. 3C) and in the interval of the two imaging tests [67.5 (16.5-151.8) days non-elderly patients vs. 66 (14-140.5) days elderly patients, $p = 0.743$] between the two groups.

No significant differences in recurrent VTE ($p = 0.194$, Fig. 4A) and clinically

relevant bleeding ($p = 0.130$, Fig. 4B) were found between the elderly and non-elderly patients. The mortality rate also did not differ significantly between the two groups ($p = 0.241$, Fig. 4C), although cancer patients were significantly more in the non-elderly group ($p = 0.038$, Table 2).

Finally, the differences in VTE recurrence, clinically relevant bleeding, and death were examined among the four groups (non-elderly or elderly and with or without cancer groups). As shown in Fig. 5A and B, recurrent VTE and clinically relevant bleeding were not significantly different among the four groups. The mortality rate was significantly higher in cancer than in non-cancer patients, regardless of age ($p < 0.001$, Fig. 5C).

## Discussion

The main findings of the present study were that the incidence of recurrent VTE and clinically relevant bleeding after the administration of Xa inhibitors for VTE treatment were comparable between cancer and non-cancer or elderly and non-elderly patients, and that the mortality rate was higher in cancer patients, with most deaths caused by cancer.

VTE is a major complication of cancer, and it is the second most common cause of

death in cancer patients.[18] The incidence of symptomatic VTE in cancer patients has been reported as 2 to 30%.[19, 20] The recurrence of VTE is also more frequent in cancer patients, in whom it is increased 4 times.[9] Tumor cells can trigger coagulation through different pathways, including procoagulant, antifibrinolytic, and pro-aggregating activities, release of pro-inflammatory and pro-angiogenic cytokines, and interaction with vascular and blood cells through adhesion molecules.[21] Not only cancer itself, but also cancer treatment, such as surgery, chemotherapy, anti-angiogenic agents, hormone therapy, and indwelling central venous catheters, and the demographics and comorbidity of patients contribute to the development of VTE.[22] Therefore, cancer patients are at high risk of VTE. Cancer also enhances the risk of anticoagulant-induced bleeding, even when anticoagulation is appropriately controlled.[9] Anticoagulants with less recurrent VTE and bleeding are required for the treatment of VTE in patients with cancer. Currently, the guidelines from the US and Europe recommend low-molecular weight heparin (LMWH)-based therapy over warfarin-based therapy as an initial and a long-term treatment for VTE in cancer patients.[23] Recently, two trials in which the effects of oral factor Xa inhibitors and dalteparin, an LMWH, on VTE treatment were compared in a head-to-head manner in cancer patients were reported. The Hokusai VTE Cancer trial showed that edoxaban

was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent VTE or major bleeding.[24] In the SELECT-D trial, VTE recurrence was relatively lower, but clinically relevant non-major bleeding was higher with rivaroxaban therapy than with dalteparin therapy.[25] These suggest that Xa inhibitors are clinically useful and alternative anticoagulants for the treatment of VTE in cancer patients, given that oral administration is more convenient than daily subcutaneous injections. However, LMWH is not approved for VTE therapy in Japan; therefore, the effectiveness and safety of Xa inhibitors in VTE treatment were compared between cancer and non-cancer patients. In the present study, the demographics of patients and the proportion of PE were similar in patients with and without cancer, although DVT at the proximal legs and upper site was more common in patients with than without cancer. With this background, VTE recurrence and clinically relevant bleeding were comparable between the two groups. Death was significantly more common in cancer than non-cancer patients, though most causes of death were cancer, not VTE- and bleeding-related deaths. These findings suggest that Xa inhibitors may be a first-line anticoagulant therapy for VTE in cancer patients in Japan.

The elderly have a higher incidence of VTE, and various age-related demographic characteristics are associated with VTE occurrence, such as general frailty, surgery,

hospitalization, nursing home confinement, trauma, neurologic disease, previous VTE, indwelling of central venous catheters, and cancer.[26] However, it is not still clear how prothrombotic factors relate to the age-related increase in thrombosis risk. Regarding the coagulation system, circulating D-dimer, factor VIII, and thrombin fragment F 1+2 increase with age, although the association with VTE is not known.[27] On the other hand, elderly patients with VTE have a higher incidence of bleeding complications on therapeutic doses of anticoagulant therapy.[28] VKAs have been used for the prevention and treatment of VTE. In patients ≥ 75 years, the incidence of VKA-related bleeding increases to 5% per year.[29] In treatment using VKAs in elderly patients, there are many problematic and age-related factors, such as drug interactions, malnutrition, liver dysfunction, dehydration, and hypertension, which complicate the achievement of the target prothrombin time internationalized ratio.[28] Large randomized trials of VTE treatment have shown that Xa inhibitors had non-inferiority for recurrent VTE and a trend to a lesser incidence of major bleeding compared with VKAs.[11-14] A meta-analysis including these trials demonstrated that Xa inhibitors were associated with superiority for recurrent VTE and VTE-related deaths in VTE patients aged ≥75 years, and no difference in bleeding events.[30] These suggest that Xa inhibitors are more useful agents for VTE treatment in elderly patients at high risk of VTE and

treatment-related bleeding. The results of the present study showed no differences in VTE recurrence, clinically relevant bleeding, and death between non-elderly and elderly patients. This suggests that Xa inhibitors are useful for VTE treatment irrespective of age.

In elderly patients, cancer is considered to be a predictor of VTE recurrence[27], bleeding[31], and mortality[32]. However, Lauber et al. reported that only two factors, unprovoked VTE and proximal DVT, were independently associated with recurrent VTE, indicating that traditional risk factors for VTE recurrence (eg, cancer) may be less relevant in elderly patients.[33] Thus, VTE recurrence, clinically relevant bleeding, and death were compared among four groups: non-elderly patients without cancer; elderly patients without cancer; non-elderly patients with cancer; and elderly patients with cancer. As shown in Fig. 5, no significant differences in these outcomes were found among the four groups, although cancer was more frequent in non-elderly than in elderly patients. Collectively, the present study suggests that Xa inhibitors may be promising agents for the treatment of VTE irrespective of age and having cancer, when adhering to the administration regime. To clarify the efficacy and safety of Xa inhibitors for VTE treatment in elderly and cancer patients, prospective, randomized, controlled trials with large cohorts will be required.

**Limitations**

This study was a retrospective, observational study evaluating a small population at a single institution. The changes in thrombosis were judged by comparing the changes on two imaging tests performed before and after Xa inhibitor treatment, irrespective of the absolute amount of thrombus or the VTE site before Xa inhibitor therapy. Because the analyses were based on a chart review in our hospital, events that were not recorded by doctors and paramedical personnel could not be analyzed. In addition, the events, recurrent VTE and clinically relevant bleeding, were analyzed only during the administration of Xa inhibitors and after stopping them within 1 week, because the goal was to examine the direct effects of Xa inhibitors on these events. The proportions of the administered Xa inhibitors differed, which was due to the difference in approval dates for VTE treatment of each agent.

In conclusion, the present study demonstrated that the effectiveness and safety of Xa inhibitors for VTE treatment were comparable among elderly/non-elderly patients with or without cancer. Therapy with Xa inhibitors may be clinically useful regardless of age and comorbid cancer.

## Conflict of interest

Satoshi Ikeda received lecture fees from Daiichi-Sankyo, Bayer, Bristol-Myers Squibb, and Pfizer. Masamichi Eguchi received a research grant from Daiichi-Sankyo. Koji Maemura received lecture fees from Daiichi-Sankyo, Bayer, Bristol-Myers Squibb, and Pfizer, and research grants from Daiichi-Sankyo, Bayer, Bristol-Myers Squibb, Pfizer, and Eisai.

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**Figure legends**

**Fig. 1** Comparison of the type of venous thromboembolism (deep vein thrombosis alone or with pulmonary thromboembolism) (A), the site of deep vein thrombosis (B), and the changes in thrombus amount (C) between cancer and non-cancer patients. DVT, deep vein thrombosis; PE, pulmonary thromboembolism; Proximal, thrombosis between the inferior vena cava and knee joint; Distal, thrombosis below the knee joint; Upper, thrombosis between the superior vena cava and upper extremities. Normalized, no thrombus in the legs and lungs; Improved, improved results for both legs and lungs, or improvement for either legs or lungs without deterioration at the other site; Unchanged, unchanged results for both legs and lungs.

**Fig. 2** Comparison of the cumulative incidence of recurrent venous thromboembolism (A), clinically relevant bleeding (B), and death (C) between cancer and non-cancer patients.

**Fig. 3** Comparison of the type of venous thromboembolism (deep vein thrombosis alone or with pulmonary thromboembolism) (A), the site of deep vein thrombosis (B), and the changes in thrombus amount (C) between elderly and non-elderly patients. Abbreviations as in Fig. 1.

**Fig. 4** Comparison of the cumulative incidence of recurrent venous

thromboembolism (A), clinically relevant bleeding (B), and death (C) between elderly and non-elderly patients.

**Fig. 5** Comparison of the cumulative incidence of recurrent venous thromboembolism (A), clinically relevant bleeding (B), and death (C) among elderly or non-elderly patients with and without cancer.

**Table 1. Characteristics of cancer and non-cancer patients with venous thromboembolism.**

| | Non-cancer | Cancer | p-value |
|---|---|---|---|
| Gender (male: female) | 39: 56 | 32: 60 | 0.380 |
| Age (years) | 68 (56-78) | 67 (60-73) | 0.537 |
| Body weight (kg) | 58.5 ± 13.8 | 57.2 ± 13.2 | 0.535 |
| Body mass index ($kg/m^2$) | 23.3 ± 4.4 | 22.9 ± 4.5 | 0.549 |
| Creatinine clearance (ml/min) | 66.2 (50.0-99.5) | 72.5 (53.9-88.9) | 0.704 |
| D-dimer (μg/ml) | 4.35 (1.70-14.10) | 5.70 (3.20-10.60) | 0.234 |
| Administration duration (days) | 51 (13-218) | 77 (23-189) | 0.873 |

Variables are expressed as mean ± SD or medians (interquartile 25% and 75%).

**Table 2. Characteristics of elderly and non-elderly patients.**

| | Non-elderly | Elderly | p-value |
|---|---|---|---|
| Gender (male: female) | 54: 76 | 17: 40 | 0.143 |
| Age (years) | 63 (54-68) | 79 (77-82) | < 0.001 |
| Body weight (kg) | 59.9 ± 13.9 | 53.3 ± 11.1 | 0.002 |
| Body mass index (kg/m$^2$) | 23.4 ± 4.7 | 22.5 ± 3.9 | 0.185 |
| Creatinine clearance (ml/min) | 82.3 (59.7-105.1) | 53.7 (44.2-63.3) | < 0.001 |
| D-dimer (μg/ml) | 4.50 (2.13-11.33) | 5.70 (3.55-15.05) | 0.260 |
| Administration duration (days) | 67 (18-206) | 80 (17-195) | 0.419 |
| Cancer (-: +) | 57: 73 | 35: 22 | 0.038 |

Variables are expressed as mean ± SD or medians (interquartile 25% and 75%).

Fig. 1

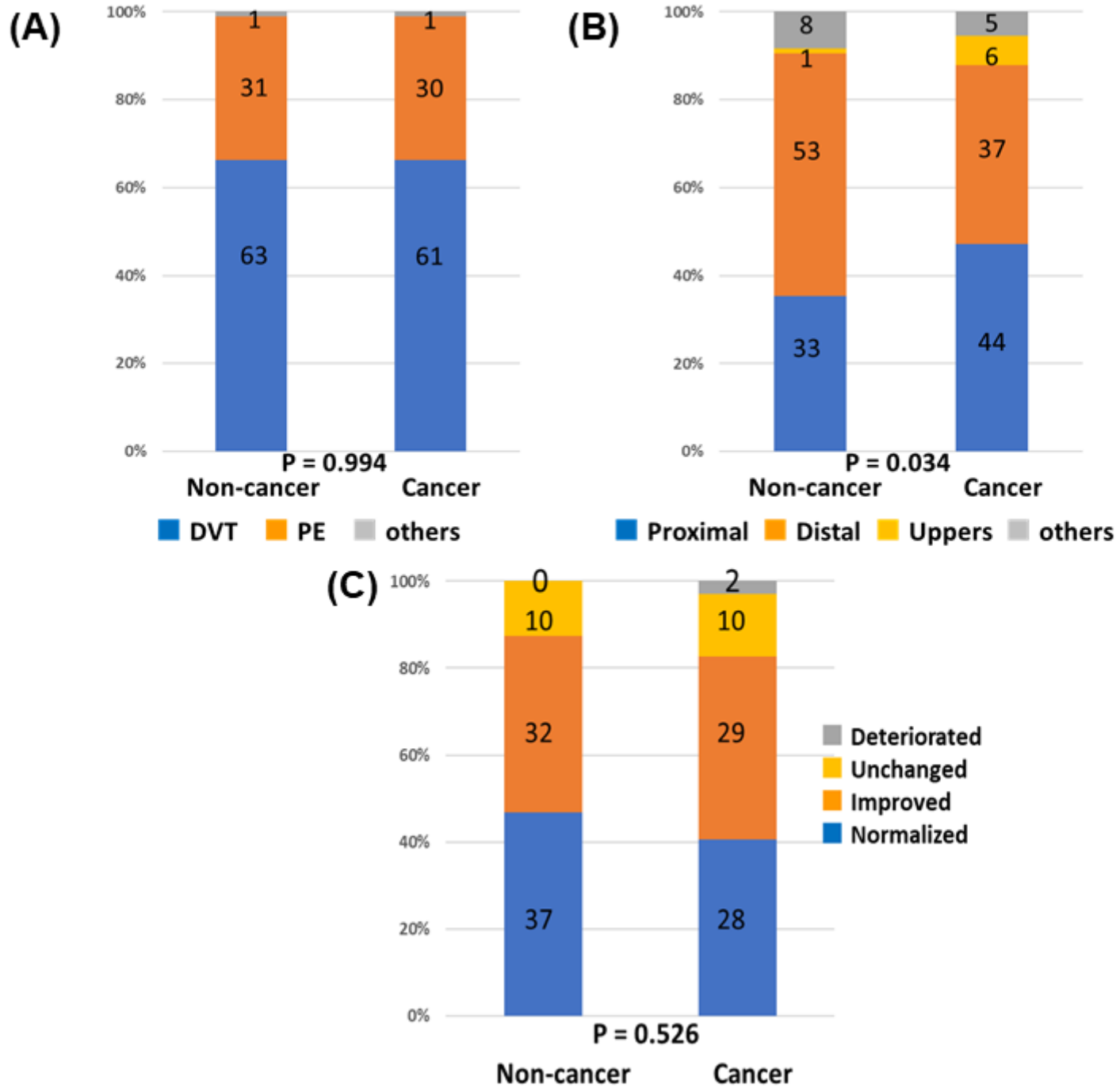

(A)
100%
80%
60%
40%
20%
0%
1
31
63
1
30
61
P = 0.994
Non-cancer
Cancer
DVT
PE
others
(B)
8
1
53
33
5
6
37
44
P = 0.034
Non-cancer
Cancer
Proximal
Distal
Uppers
others
(C)
0
10
32
37
2
10
29
28
P = 0.526
Non-cancer
Cancer
Deteriorated
Unchanged
Improved
Normalized

Fig. 2

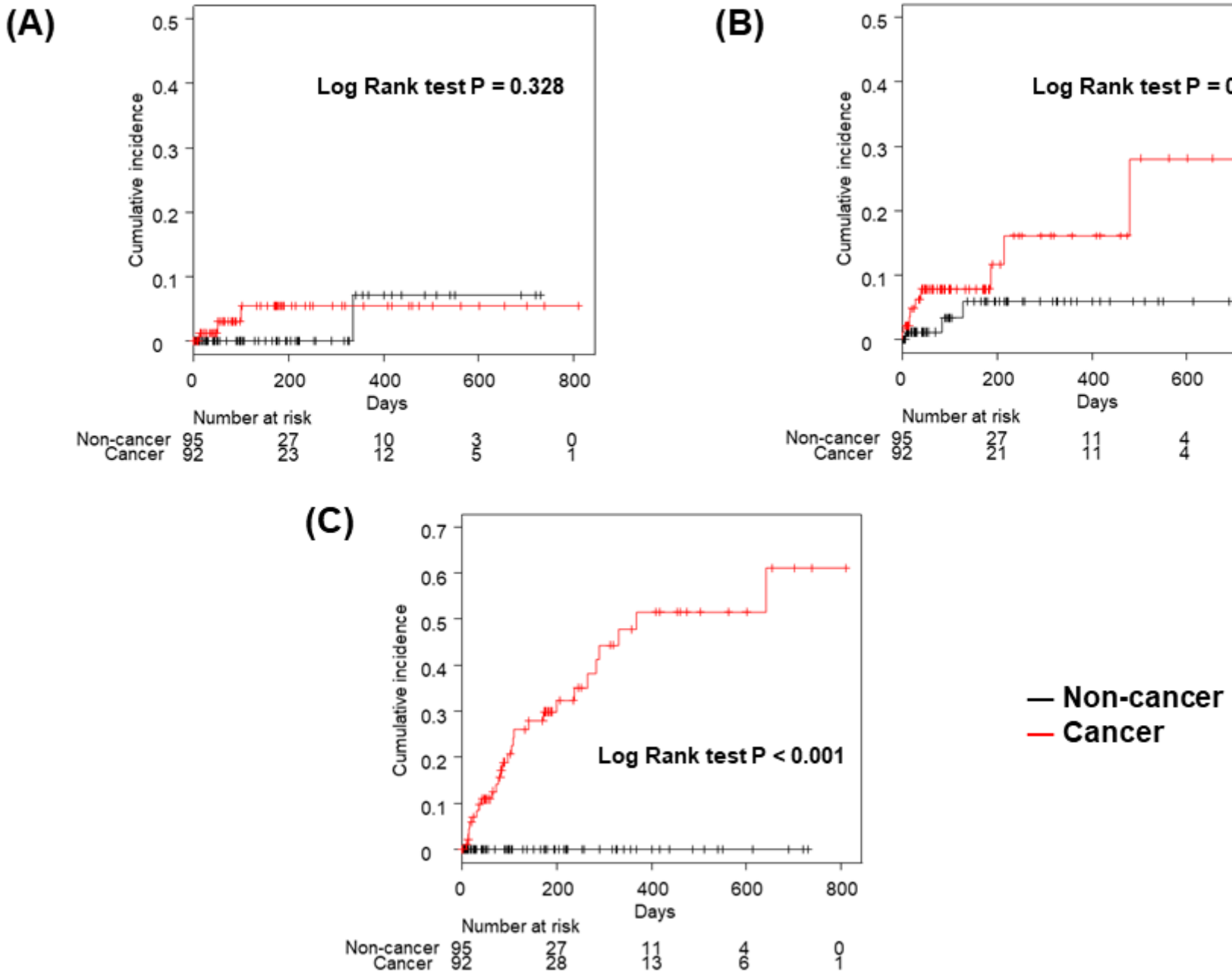

(A)
Log Rank test P = 0.328
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-cancer 95 27 10 3 0
Cancer 92 23 12 5 1
(B)
Log Rank test P = 0.078
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-cancer 95 27 11 4 0
Cancer 92 21 11 4 1
(C)
Log Rank test P < 0.001
Cumulative incidence
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-cancer 95 27 11 4 0
Cancer 92 28 13 6 1
Non-cancer
Cancer

Fig. 3

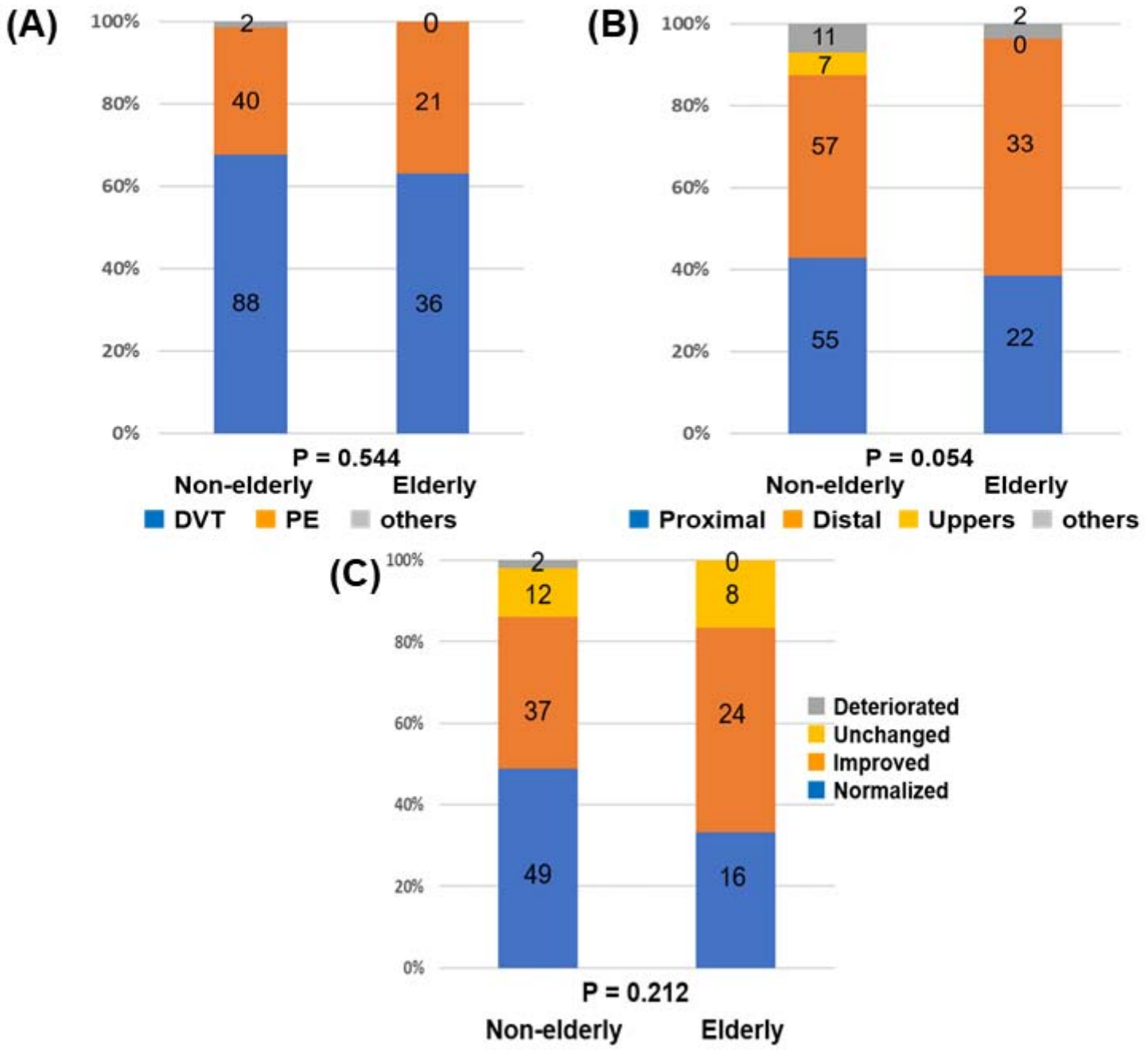

(A)
100%
80%
60%
40%
20%
0%
2
40
88
0
21
36
P = 0.544
Non-elderly
Elderly
DVT
PE
others
(B)
11
7
57
55
2
0
33
22
P = 0.054
Non-elderly
Elderly
Proximal
Distal
Uppers
others
(C)
2
12
37
49
0
8
24
16
P = 0.212
Non-elderly
Elderly
Deteriorated
Unchanged
Improved
Normalized

Fig. 4

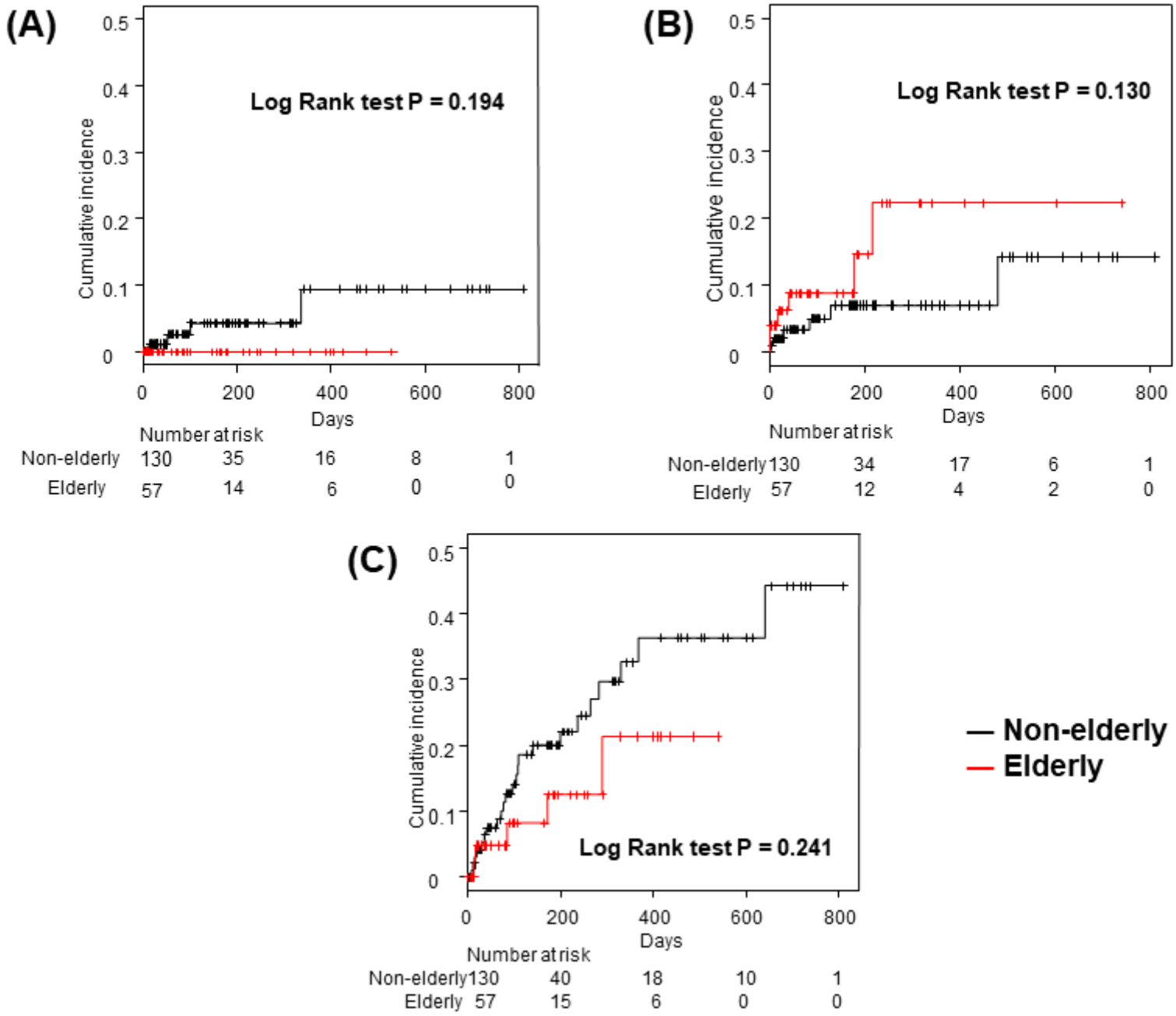
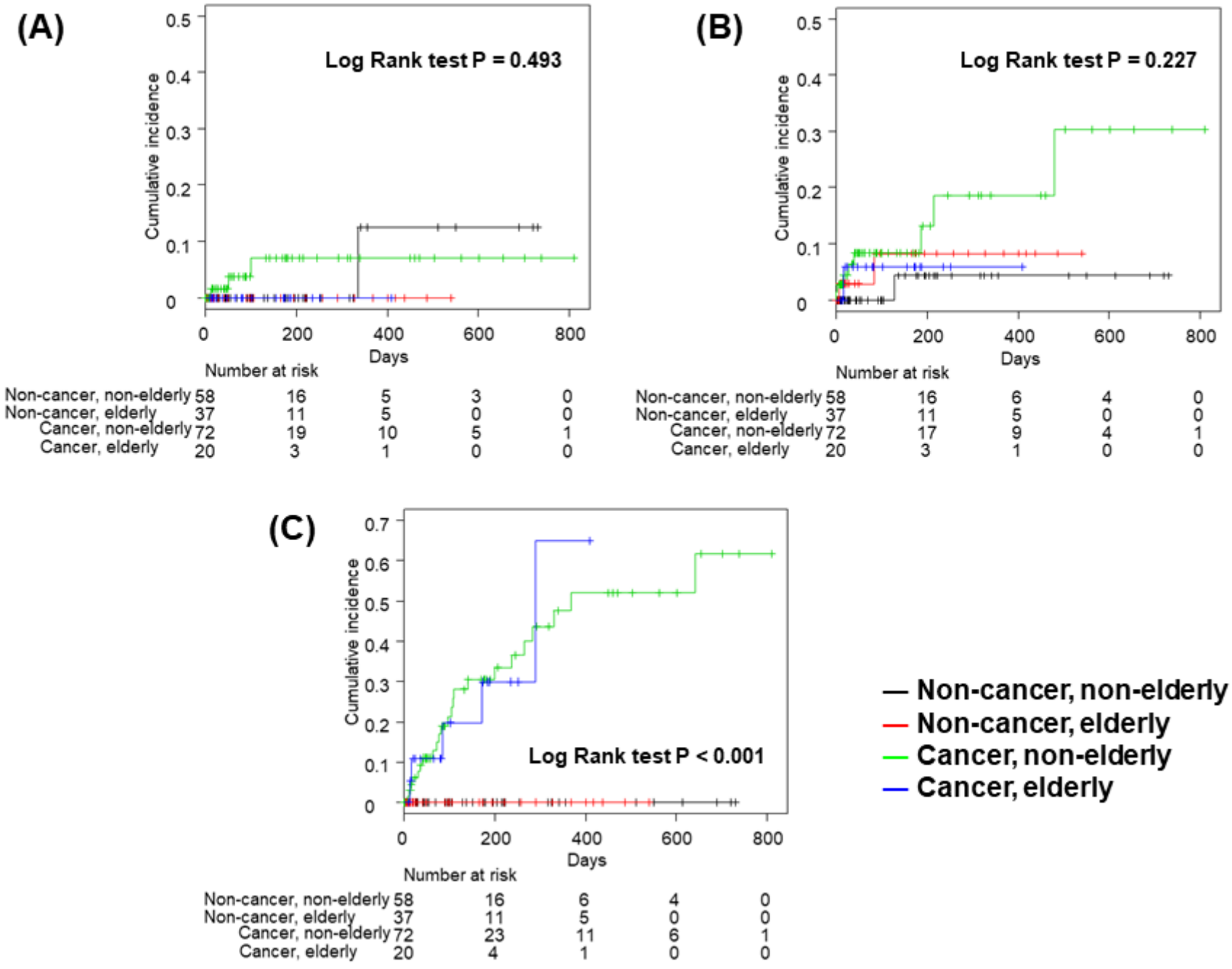

(A)
Log Rank test P = 0.194
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-elderly 130 35 16 8 1
Elderly 57 14 6 0 0
(B)
Log Rank test P = 0.130
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-elderly 130 34 17 6 1
Elderly 57 12 4 2 0
(C)
Log Rank test P = 0.241
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-elderly 130 40 18 10 1
Elderly 57 15 6 0 0
Non-elderly
Elderly

Fig. 5


(A)
Log Rank test P = 0.493
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-cancer, non-elderly 58 16 5 3 0
Non-cancer, elderly 37 11 5 0 0
Cancer, non-elderly 72 19 10 5 1
Cancer, elderly 20 3 1 0 0
(B)
Log Rank test P = 0.227
Cumulative incidence
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-cancer, non-elderly 58 16 6 4 0
Non-cancer, elderly 37 11 5 0 0
Cancer, non-elderly 72 17 9 4 1
Cancer, elderly 20 3 1 0 0
(C)
Log Rank test P < 0.001
Cumulative incidence
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
200
400
600
800
Days
Number at risk
Non-cancer, non-elderly 58 16 6 4 0
Non-cancer, elderly 37 11 5 0 0
Cancer, non-elderly 72 23 11 6 1
Cancer, elderly 20 4 1 0 0
Non-cancer, non-elderly
Non-cancer, elderly
Cancer, non-elderly
Cancer, elderly