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Original Article

Association between patient's age and the utility of prognostic markers after pancreaticoduodenectomy for pancreatic cancer

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A B S T R A C T

Background & aims: Optimizing treatments balancing prognosis and therapeutic invasiveness is important in the management of pancreatic cancer (PC) owing to global ageing. This study aimed to verify the different utility of biomarkers by patients' age.

Materials & methods: This is a single-center, retrospective cohort analysis involving 160 patients who undertook pancreaticoduodenectomy (PD) for PC. After comparing clinicopathological factors and survival after PD between aged (≥70 y/o) and young (<70 y/o) patients, we compared neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), controlling nutrition (CONUT) score, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19–9 as well as clinicopathological factors between long and short survivors in each group. We also performed Kaplan-Meyer analysis between patients stratified by biomarkers.

Results: Overall survival (OS) was significantly worse in aged patients ($p = 0.002$). In aged patients, CEA was significantly higher in short survivors. In young patients, CONUT score and CA19-9 were higher in short survivors. Kaplan-Meyer analysis showed that NLR and CEA stratified OS in aged patients, whereas CONUT score and CA19-9 could stratify OS in young patients.

Conclusion: Our current results suggest that these biomarkers had different impact on survivals according to the patients' age.

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1. Introduction

Pancreatic cancer (PC) is one of the common causes of cancer death in Western societies.[1] Although lots of efforts to improve prognosis has been paid, its overall 5-year survival rate is still <5%.[2] The mainstay of treatment for PC is surgery, but pancreatic resection causes postoperative complications with high incidence.[3] In addition, the 5-year overall survival (OS) even in patients who undertook curative surgery is no more than 30%.[4] Thus, optimizing treatment for each patient balancing expected prognosis, quality of life and invasiveness of therapies is important.

Ageing is one of the important problems we have to face when applying surgery for PC. During the past 200 years, the average human life expectancy has doubled in developed countries, and survival rates of elderly persons and mean life expectancy are projected to continue to increase.[5] There is a strong positive correlation between advancing age and the incidence of PC, indicating elderly candidates for pancreatic resection will increase.[6] Because of frailty and multiple comorbidities,[7,8] some investigators have revealed that the prognosis after pancreaticoduodenectomy (PD) was worse in the elderly.[9] Therefore, reasonable selection of older patients with PC for aggressive treatments is important not only for their own recovery, but also from the perspective of medical economics.

A lot of studies have tried to stratify patients with PC using various kinds of biomarkers. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9) are widely used in the diagnosis of PC and reported to be useful also in predicting prognosis.[10,11] Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are also studied as a low-cost tool of

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stratification.[11–14] Recently, Kato et al suggested controlling nutritional status (CONUT) score as a useful tool of predicting prognosis after pancreatic resection.[15] Considering the physiological and biological difference between young and older persons, we hypothesized that the utility of biomarkers might different according to the patient's age.

In this study, we compared prognosis after PD for PC between aged (≥70 years old; y/o) and young (<70 y/o) patients. Then we evaluated the prognostic value of several biomarkers for each group separately.

2. Methods

2.1. Patients

Patients with PC who were operated at Kyoto University Hospital (Kyoto, Japan) during January 2006 and December 2015 were enrolled in this retrospective study. Data on patients' background characteristics (age, sex, comorbidities), body mass index (BMI), treatment with adjuvant chemotherapy, operation-related variables (intraoperative blood loss, operative time, performance of transfusion), and pathological data were obtained from the medical records. This study was approved by the Ethics Committee of Kyoto University (approved number: R0455) and performed in accordance with the ethical standards of the revised Helsinki Declaration of 2013.

2.2. Operative procedures

All operative procedure**s** of PD were performed in the same way which have been described previously.[16] Briefly, PD was performed using any of the classic methods depending on the extent of the disease (pylorus-preserving PD or subtotal stomach-preserving PD). After dissection of the mesenteric lymph nodes, Kocher's mobilization, and dissection of the hepatoduodenal ligament, the pancreas was divided anteriorly. Then, the pancreatic head nerve plexus was dissected. If the portal vein or superior mesenteric vein was invaded, combined resection and reconstruction of the vessels was performed. Pancreatojejunostomy, choledochojejunostomy, and antecolic reconstruction of the alimentary tract were subsequently performed. Two closed suction tubes were placed behind the biliary and pancreatic anastomosis.

The details of perioperative management, such as administration of antibiotics, taking blood samples and drainage fluid, and removal of drains, were the same as previously described.[16]

Patients who undertook neoadjuvant therapy were excluded from the analysis. In principle, adjuvant chemotherapy with S-1 or gemcitabine were performed as far as possible.

2.3. Definitions of complications

Early complications were defined as morbidities that occurred in the course of the postoperative admission. Postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE) were diagnosed according to the criteria of the International Study Group on Pancreatic Fistula (ISGPF).[17,18] Other complications were recorded when their grade was greater than III in the Clavien-Dindo classification.

Late complications were defined as those that occurred after discharge. Diarrhea was recorded when the patient complained of the symptom. Malnutrition was defined as weight loss of greater than 10% of preoperative weight. Other complications were counted based on the patients' reports.

2.4. Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) or medians (interquartile range), as appropriate. Comparisons between groups were performed by the χ^2-test (categorical variables) or the Wilcoxon test (continuous variables). Cut-off values of NLR and CONUT score were determined by ROC curves, whereas cut-off values of CEA (5.0 ng/ml) and CA19-9 (37.0 U/ml) were determined by upper limit of normal range in our institution. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. $P < 0.05$ was considered significant.

3. Results

3.1. Comparisons of patients' background characteristics, operation-related and pathological factors between aged (≥70 years old) and young (<70 years old) patients

Curative PD was performed for 176 patients during the study period. 16 patients were excluded because they received neoadjuvant chemoradiotherapy due to arterial invasion. No 30-day mortality was observed. Among total of 160 patients, the median age of total population was 69 years old and there were 75 patients (47%) in the aged (≥70 years old: y/o) group and 85 (53%) patients in the young (<70 y/o) group. Comparisons of patients' characteristics between two groups were shown in Table 1. The rate of patients whose American Society of Anesthesiologists - Physical Status (ASA-PS) above grade 2 was 64% (48/64) in the aged group, whereas 49% (42/85) in the young group ($p = 0.063$). Preoperative nutritive scores such as body mass index (Aged: Young, 21.6 ± 3.0: 21.7 ± 3.4, $p = 0.911$) and CONUT score (2.7 ± 2.1:2.4 ± 2.0, $p = 0.302$) were not statistically different. Similarly, tumor markers such as CEA (4.1 ± 3.1:4.3 ± 8.1 [ng/ml], $p = 0.078$) and CA19-9 (230.3 ± 387.6:222.7 ± 461.4 [U/ml], $p = 0.441$) were comparable between two groups.

As for the operation-related parameters, intraoperative bleeding (median, 800:760 [ml], $p = 0.918$), operative time (566 ± 95:577 ± 123 [minutes], $p = 0.885$) and postoperative hospital inpatient days (35 ± 18:36 ± 21 [days], $p = 0.401$) were almost equal. Noteworthy, the prevalence of early complications above grade III in Clavien-Dindo classification (12%:18%, $p = 0.315$) and late complications (25%:20%, $p = 0.421$) were not statistically different. Importantly, adjuvant therapy was administered in 71% (53/75) of patients in aged group, whereas 92% (78/85) in the young group ($p < 0.001$).

Pathologically, the mean diameter of the tumor (3.6 ± 4.6:3.5 ± 4.4 [cm], $p = 0.840$) and the prevalence of the regional lymph nodes (56%:56%, $p = 0.952$) and portal vein involvement (23%:24%, $p = 0.897$) were not statistically different.

3.2. Survival analysis comparing two age groups

Next, recurrence-free survival (RFS) and overall survival (OS) after PD were compared between aged and young groups. The median RFS was 9 (interquartile range: 5–19) months in the aged group and 11 (5–39) months in the young group ($p = 0.220$). On the other hand, median OS was significantly worse in aged group (elderly: young, 18 (11–35):28 (16–66) [months], $p = 0.007$). Kaplan–Meier analysis showed no significant difference in RFS ($p = 0.084$, Fig. 1A), whereas OS was worse in aged group ($p = 0.002$, Fig. 1B).

3.3. Analysis of factors associated with survival in the elderly group

We assessed the utility of prognostic indicators such as NLR, PLR,

Table 1
Comparisons of characteristics between aged (≥70 y/o) and young (<70 y/o) patients. Continuous variables were indicated as mean ± standard deviation).

	Aged	Young	P
	n = 75	n = 85	
Preoperative factors			
Sex, female (%)	32 (43)	42 (57)	0.393
ASA-PS ≥ 2 (%)	48 (64)	42 (49)	0.063
Body mass index [kg/m^2]	21.6 (3.0)	21.7 (3.4)	0.911
CONUT score	2.7 ± 2.1	2.4 ± 2.0	0.302
CEA [ng/ml]	4.1 ± 3.1	4.3 ± 8.1	0.078
CA19-9 [U/ml]	230.3 ± 387.6	222.7 ± 461.4	0.441
Operation-related factors			
Intraoperative bleeding [ml], median (range)	800 (200–3872)	760 (150–4980)	0.918
Operation time [min]	566 ± 95	577 ± 123	0.885
Postoperative stay [days]	35 ± 18	36 ± 21	0.401
Early complication ≥ CD3 (%)	9 (12)	15 (18)	0.315
Late complication (%)	19 (25)	17 (20)	0.421
Pathological factors			
Tumor diameter [cm]	3.6 ± 4.6	3.5 ± 4.4	0.840
Involvement of portal vein (%)	17 (23)	20 (24)	0.897
Involvement of lymph nodes (%)	42 (56)	48 (56)	0.952
Adjuvant therapy (%)	53 (71)	78 (92)	<0.001*

ASA-PS; American Society of Anesthesiologists -Physical Status, CONUT; Controlling Nutritional Status, CEA; Carcinoembryonic antigen, CA19-9; Carbohydrate antigen 19–9, CD; Clavien-Dindo classification.

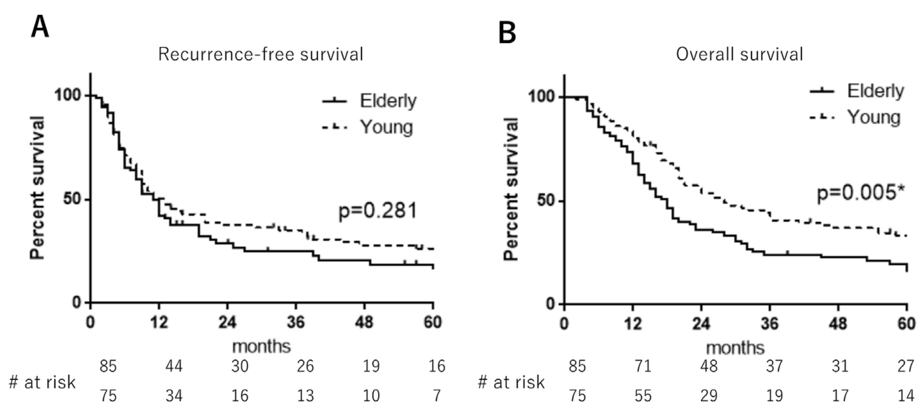

Fig. 1. Comparison of survival curves for recurrence-free survival (A) and overall survival (B) after pancreaticoduodenectomy in patients with pancreatic cancer.

CONUT score as well as CEA and CA19-9 in each age group separately. Because the median OS of the whole study population was 21 months, we divided aged and young patients into two groups: patients who survived longer (long survivors of aged: LS-A, long survivors of young: LS-Y) and shorter (short survivors of aged: SS-A, short survivors of young: SS-Y) than 21 months.

The comparison of SS-A and LS-A were shown in Table 2. The value of CEA was significantly higher in SS-A (SS-A:LS-A, 5.0 ± 3.6:2.9 ± 1.5 [ng/ml], p = 0.010), whereas no significant differences were observed in the mean level of NLR (2.9 ± 1.2:2.6 ± 1.4, p = 0.140), PLR 165.7 ± 5.7:140.1 ± 168.2, p = 0.263), CONUT score (3.0 ± 2.4:2.2 ± 1.5, p = 0.211) and CA19-9 (288.4 ± 471.7:140.1 ± 168.2 [U/ml], p = 0.877).

We also compared operation-related and pathological factors between LS-A and SS-A. The rate of intraoperative transfusion was not significantly different (31%:13%, p = 0.069), but the operative time was longer in SS-A (592 ± 92:527 ± 86 [min], p = 0.004). The prevalence of late complication was higher in SS-A (36%:10%, p = 0.009), whereas no difference was detected about early complications above grade III in Clavien-Dindo classification (16%:7%, p = 0.230). Noteworthy, pathological parameters such as tumor diameter (4.2 ± 5.9:2.7 ± 0.9 [cm], p = 0.274), the rate of portal vein (27%:17%, p = 0.304) or lymph node involvement (58%:53%, p = 0.704) were comparable between the two groups. The

Table 2
Comparisons of characteristics of patients ≥70 y/o between short and long survivors after pancreaticoduodenectomy. Continuous variables were indicated as mean ± standard deviation).

	SS-A	LS-A	P
	n = 45	n = 30	
Sex, female (%)	18 (40)	14 (47)	0.568
NLR	2.9 ± 1.2	2.6 ± 1.4	0.140
PLR	165.7 ± 5.7	151.0 ± 6.6	0.263
CONUT score	3.0 ± 2.4	2.2 ± 1.5	0.211
CEA	5.0 ± 3.6	2.9 ± 1.5	0.004*
CA19–9	288.4 ± 471.7	140.1 ± 168.2	0.877
Intraoperative blood loss [ml]	1133 ± 809	896 ± 666	0.136
Operation time [min]	592 ± 92	527 ± 86	0.004*
Early complication ≥ CD3 (%)	7 (16)	2 (7)	0.230
Late complication (%)	16 (36)	3 (10)	0.009*
Resection with residual tumor (%)	9 (20)	5 (17)	0.715
Tumor diameter [cm]	4.2 ± 5.9	2.7 ± 0.9	0.274
Involvement of portal vein (%)	12 (27)	5 (17)	0.304
Involvement of lymph nodes (%)	26 (58)	16 (53)	0.704
Adjuvant therapy (%)	30 (67)	23 (77)	0.347

SS-A; short survivor of aged, LS-A; long survivor of aged, NLR; neutrophil-lymphocyte ratio, PLR; platelet-lymphocyte ratio, CONUT; Controlling Nutritional Status, CEA; carcinoembryonic antigen, CA19-9; carbohydrate antigen 19–9, CD; Clavien-Dindo classification.

Table 3
Comparisons of characteristics of patients < 70 y/o between short and long survivors after pancreaticoduodenectomy. Continuous variables were indicated as mean ± standard deviation).

	SS-Y	LS-Y	P
	n = 34	n = 51	
Sex, female (%)	12 (35)	30 (59)	0.033*
NLR	2.8 ± 2.0	2.4 ± 1.2	0.481
PLR	173.5 ± 6.7	169.7 ± 6.6	0.670
CONUT score	2.9 ± 2.0	2.1 ± 1.9	0.033*
CEA [ng/ml]	3.6 ± 2.0	4.8 ± 10.2	0.104
CA19–9 [U/ml]	301.5 ± 578.4	171.6 ± 364.1	0.049*
Intraoperative blood loss [ml]	1451 ± 1257	849 ± 566	0.031*
Operation time [min]	603 ± 136	559 ± 111	0.089
Early complication ≥ CD3 (%)	6 (18)	9 (18)	1.000
Late complication (%)	6 (18)	11 (22)	0.656
Resection with residual tumor (%)	8 (23)	8 (16)	0.369
Tumor diameter [cm]	4.4 ± 5.7	2.8 ± 2.9	<0.001*
Involvement of portal vein (%)	13 (38)	7 (14)	0.010*
Involvement of lymph nodes (%)	26 (76)	22 (43)	0.002*
Adjuvant therapy (%)	32 (94)	46 (90)	0.511

SS-A; short survivor of aged, LS-A; long survivor of aged, NLR; neutrophil-lymphocyte ratio, PLR; platelet-lymphocyte ratio, CONUT; Controlling Nutritional Status, CEA; carcinoembryonic antigen, CA19-9; carbohydrate antigen 19–9, CD; Clavien-Dindo classification.

population of patients who were treated with adjuvant chemotherapy was not statistically different (67%:77%, p = 0.347).

3.4. Analysis of factors associated with survival in the young group

Similarly, we compared serological, operation-related and pathological factors between LS-Y and SS-Y (Table 3). The CONUT score was significantly higher in SS-Y (SS–Y:LS-Y, 2.9 ± 2.0:2.1 ± 1.9, p = 0.033), whereas NLR (2.8 ± 2.0:2.4 ± 1.2, p = 0.481) and PLR (173.5 ± 6.7:169.7 ± 6.6, p = 0.670) were not different. Unlike elderly, CA19-9 was higher in SS-Y, whereas CEA was not significantly different.

Intraoperative blood loss (1451 ± 1257:849 ± 566 [ml], p = 0.031) and the rate of blood transfusion (18%:4%, p = 0.035) was higher in SS-Y group. Pathologically, tumor diameter, the rate of portal vein and lymph node involvement were higher in SS-Y than LS-Y. The rate of adjuvant therapy was almost equal (94%:90%, p = 0.511).

3.5. Kaplan-Meyer analysis of each group stratified by preoperative serological markers

Figs. 2 and 3 represents survival curves of elderly and young patients stratified by NLR, CONUT score, CEA and CA19-9. The cut-off values of NLR (2.3) and CONUT score (3) was determined by ROC analysis of total study population in predicting early recurrence. The cut-off values of CEA (5.0) and CA19-9 (37.0) was set to the upper limit of standard value in our institute. As Fig. 2 shows, survival was worse in elderly patients whose NLR and CEA was higher than the cut-off values. On the contrary, in young patients, survival was worse in patients whose CONUT score and CA19-9 was higher than the cut-off value, whereas no significant difference was shown by stratifying patients with NLR or CEA.

4. Discussion

In this study, we confirmed OS after PD for PC was significantly worse in aged patients (≥70 y/o) at first. Then we analyzed the utility of prognostic factors in aged and younger patients separately. In the aged patients, higher NLR and CEA were shown to be prognostic markers for worse OS in Kaplan-Meyer analysis. On the other hand, in young people, CONUT score and CA19-9 seemed to be useful in distinguishing patients by their prognosis. These findings might help establishing better perioperative managements according to the patient's age. Additionally, it could be useful in stratifying patients eligible for neoadjuvant or adjuvant treatment with reference to these markers.

We revealed the OS was significantly worse in the older patients. Considering the fact that RFS was not different among age groups, this could be explained by two possible reasons. One possibility is that older patients were difficult to treat when recurrence had occurred. Indeed, older group tended to have higher PS grades in our study. Although significant progress in survival has been made by combination chemotherapy in PC, the appropriate approach to dose reduction or schedule modification continues to be investigated.[19] The other possibility is that some subclinical change related to the operative procedures after PD might cause the worse survival outcome. For example, Maxwell et al showed that approximately 17% of patients after PD developed diabetes.[20] Nagaya et al reported the possible mechanisms of steatosis after PD.[21] However, these changes do not appear to affect survival in

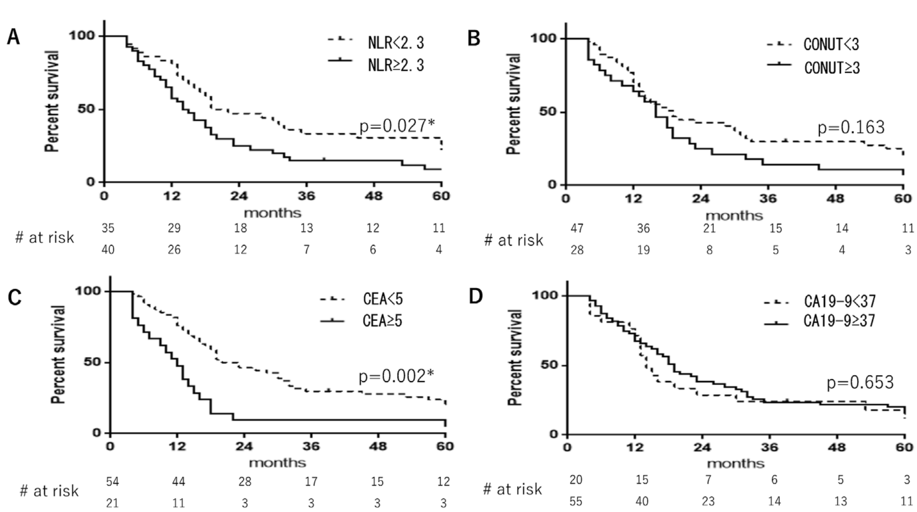

Fig. 2. Overall survival curves of aged (≥70 years old) patients stratified by cut-off values of each prognostic marker. A) NLR, B) CONUT score, C) CEA, D) CA19-9. The cut-off values of NLR and CONUT score were set to 2.3 and 3 according to the ROC analysis, whereas the cut-off values of CEA and CA19-9 were set to 5.0 and 37.0 according to the upper limits of normal range in our institute.

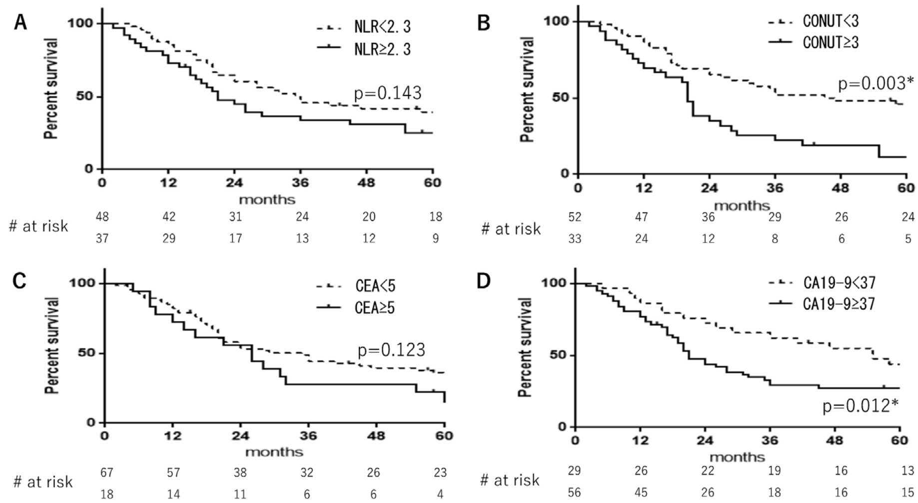

Fig. 3. Overall survival curves of young (<70 years old) patients stratified by cut-off values of each prognostic marker. A) NLR, B) CONUT score, C) CEA, D) CA19-9. The cut-off values of NLR and CONUT score were set to 2.3 and 3 according to the ROC analysis, whereas the cut-off values of CEA and CA19-9 were set to 5.0 and 37.0 according to the upper limits of normal range in our institute.

such a short period. In basic research, it has been suggested that ageing weakens the regeneration of pancreatic acinar cells.[22] The accumulation of these metabolic or digestive impairments and basic comorbidities in elderly patients might synergistically reduce the utility of anticancer drugs after recurrence. Comprehensive analysis of changes in proteomics or metabolomics after surgery might uncover the true relationships between ageing and status after PD.

In the present study, NLR discriminated OS after PD in older patients, whereas did not in younger patients. Although several investigators have reported the utility of NLR in stratifying survival of PC,[11–14] the appropriate way of applying NLR in the diary practice is not fully established. There are three reasons for this circumstance. First, most of the studies are retrospective. Second, cut-off values between studies are different. Third, underlying mechanism of the behavior of NLR is elusive. Indeed, some reports insisted NLR was not useful in predicting survival of PC.[23]

The reason of a difference in the utility of NLR between young and aged is unclear. We speculate the difference might be caused by an influence of the ageing of the immune system. The notion that the immune system behaves differently in older and younger people is unequivocal and this phenomenon results in greater susceptibility to several diseases in the elderly.[24] Low numbers of peripheral blood naïve CD8+ T lymphocytes is shown to be a characteristic finding of aged population, but the clinical implication is not understood as for now.[25] Relative reduction of lymphocytes (i.e. reduction of NLR) can cause relatively larger numbers of neutrophils, resulting in a worse prognosis in the elderly. Gaida et al declared that neutrophil plays an important role in the metastasis of PC since it can mediate epithelial–mesenchymal transition (EMT) of cancer by secreting elastase.[26] Although these hypotheses are still under investigation, our current results might reflect the relationships between immunosenescence and cancer progression.

On the contrary, higher CONUT score was an indicator of worse OS in young population. The CONUT score was firstly described as an efficient tool for detecting malnutrition.[27] Since then, studies have revealed the utility of CONUT score in the prediction not only of cancer prognosis but also of non-cancer diseases.[28–30] As for PC, Kato et al showed significantly short OS after some kinds of pancreatectomy in patients with CONUT score higher than 4[15]. They presented that patients with lower CONUT score have an adequate nutritional storage to tolerate with postoperative malnutrition. We consider that worse prognosis in higher CONUT group might be caused by a less tolerability for adjuvant chemotherapy or treatments after the recurrence.

There are several limitations in our study. First, because of the retrospective nature of the study design, there should be a selection bias. For example, elderly patients who received PD might be selected subjectively by each surgeon. Second, sample sizes in each group was not large enough, resulting in an insufficient statistical power. In order to overcome these limitations, a prospective, multi-institutional study might resolve the problem.

In conclusion, we demonstrated a different prognosis and patterns of stratification by biomarkers after PD for PC between elderly and young patients.

Author contributions

AS, TM and YU performed data acquisition and analysis of data. AS, AY and AK analyzed data and performed interpretation of data. AS drafted the article. AT and KN revised the manuscript for intellectual content. EH approved the version to be published.

COI disclosure

The authors declare that there is no conflict of interest.

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There are no financial supports in conducting this study.

Declaration of competing interest

The authors declare no conflict of interest.

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References

1. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to

2030: the unexpected burden of thyroid, liver and pancreas cancers in the United States. *Cancer Res*. 2014;74:2913–2921.
2. Vincent A, Herman J, Schulick R, et al. Pancreatic cancer. *Lancet*. 2011;378:607–620.
3. Kimura W, Miyata H, Gotoh M, et al. A pancreaticoduodenectomy risk model derived from 8575 cases from a national single-race population (Japanese) using a web-based data entry system: the 30-day and in-hospital mortality rates for pancreaticoduodenectomy. *Ann Surg*. 2014;259:773–780.
4. Strobel O, Neoptolemos J, Jager D, et al. Optimizing the outcomes of pancreatic cancer surgery. *Nat Rev Clin Oncol*. 2019;16:11–26.
5. Partridge L, Deelen J, Slagboom PE. Facing up to the global challenges of ageing. *Nature*. 2018;561:45–56.
6. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet*. 2013;381:752–762.
7. Turgeon J, Michaud V, Steffen L. The dangers of polypharmacy in elderly patients. *JAMA Intern Med*. 2017;177:1544.
8. Alexopoulos GS. Depression in the elderly. *Lancet*. 2005;365:1961–1970.
9. Yuan F, Essaji Y, Belley-Cote EP, et al. Postoperative complications in elderly patients following pancreaticoduodenectomy lead to increased postoperative mortality and costs. A retrospective cohort study. *Int J Surg*. 2018;60:204–209.
10. Wu L, Huang P, Wang F, et al. Relationship between serum CA19-9 and CEA levels and prognosis of pancreatic cancer. *Ann Transl Med*. 2015;3:328.
11. Asaoka T, Miyamoto A, Maeda S, et al. Prognostic impact of preoperative NLR and CA19-9 in pancreatic cancer. *Pancreatology*. 2016;16:434–440.
12. Yang J, Hu Z, Shi W, et al. Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: a meta-analysis. *World J Gastroenterol*. 2015;21:2807–2815.
13. Mowbray N, Griffith D, Hammoda M, et al. A meta-analysis of the utility of the neutrophil-to-lymphocyte ratio in predicting survival after pancreatic cancer resection. *HPB(Oxford)*. 2018;20:379–384.
14. Yu J, Ding Z, Yang Y, et al. Increased platelet-to-lymphocytes ratio is associated with poor long-term prognosis in patients with pancreatic cancer after surgery. *Medicine (Baltim)*. 2018;97, e11002.
15. Kato Y, Yamada S, Suenaga M, et al. Impact of the controlling nutritional status score on the prognosis after curative resection of pancreatic ductal adenocarcinoma. *Pancreas*. 2018;47:823–829.
16. Sato A, Masui T, Nakano K, et al. Abdominal contamination with Candida albicans after pancreaticoduodenectomy is related to hemorrhage associated with pancreatic fistulas. *Pancreatology*. 2017;17:484–489.
17. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery*. 2017;161:584–591.
18. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. 2007;142:761–768.
19. Garcia G, Odaimi M. Systemic combination chemotherapy in elderly pancreatic cancer: a review. *J Gastrointest Cancer*. 2017;48:121–128.
20. Maxwell DW, Jajja MR, Tariq M, et al. Development of diabetes after pancreaticoduodenectomy: results of a 10-year series using prospective endocrine evaluation. *J Am Coll Surg*. 2019;228, 400-12.
21. Nagaya T, Tanaka N, Kimura T, et al. Mechanism of the development of nonalcoholic steatohepatitis after pancreaticoduodenectomy. *BBA Clin*. 2015;3:168–174.
22. Watanabe H, Saito H, Rychahou PG, et al. Aging is associated with decreased pancreatic acinar cell regeneration and phosphatidylinositol 3-kinase/Akt activation. *Gastroenterology*. 2005;128:1391–1404.
23. Chawla A, Huang T, Ibrahim A, et al. Pretherapy neutrophil to lymphocyte ratio and platelet to lymphocyte ratio do not predict survival in resectable pancreatic cancer. *HPB(Oxford)*. 2018;20:398–401.
24. Sadighi Akha AA. Aging and the immune system: an overview. *J Immunol Methods*. 2018;463:21–26.
25. Yan J, Greer J, Hull R, et al. The effect of ageing on human lymphocyte subsets: comparison of males and females. *Immun Ageing*. 2010;7:4.
26. Grosse-Steffen T, Giese T, Gaida MM, et al. Epithelial-to-mesenchymal transition in pancreqatic ductal adenocarcinoma and pancreatic tumor cell lines: the role of neutrophils and neutrophil-derived elastase. *Clin Dev Immunol*. 2012;2012, 720768.
27. de Uribarri J, Gonzalez-Madrono A, de Villar NG, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp*. 2005;20:38–45.
28. Kuroda D, Sawayama H, Kurashige J, et al. Controlling Nutritional Status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. *Gastric Cancer*. 2018;21:204–212.
29. Ahiko Y, Shida J, Horie T, et al. Controlling nutritional status (CONUT) score as a preoperative risk assessment index for older patients with colorectal cancer. *BMC Cancer*. 2019;19:946.
30. Iwakami N, Nagai T, Furukawa TA, et al. Prognostic value of malnutrition assessed by Controlling Nutritional Status score for long-term mortality in patients with acute heart failure. *Int J Cardiol*. 2017;230:529–536.