Research Square

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Dynamic analysis of C-reactive protein/albumin ratio in pancreatic cancer

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Abstract

The C-reactive protein/albumin ratio (CAR), an inflammatory marker, is a useful biomarker for pancreatic cancer. Although disease status is not constant, many inflammatory markers are only classified at the start of treatment. Therefore, biomarker analysis that considers the changes in inflammatory markers during treatment is desirable. We aimed to investigate whether time-dependent changes in the CAR during nanoliposomal irinotecan with fluorouracil and folinic acid (NFF) administration can predict the prognosis of patients with unresectable or recurrent pancreatic cancer (urPC). CAR was measured in 150 participants of the NAPOLEON-2 study, an observational study involving patients with pancreatic cancer receiving NFF, and the patients were stratified by CAR. The CAR at NFF initiation was defined as CAR(1), while the minimum CAR before/throughout NFF administration was defined as CAR(min). Overall survival (OS) of patients in all groups was analyzed. Significant differences in OS between the CAR(1) < 0.54 and ≥ 0.54 groups and between the CAR(min) < 0.54 and ≥ 0.54 groups were observed. The OS was significantly better in the group with CAR(min)/CAR(1) < 0.5 than in the group with CAR(min)/CAR(1) ≥ 0.5. Dynamic changes in CAR were a clinically significant biomarker that considers not only the disease status at the start of treatment but also the response to treatment. CAR monitoring would help understand the disease status and thereby aid patients and physicians alike.

Introduction

Pancreatic cancer has worse prognosis than other cancers and is the sixth leading cause of cancer-related deaths worldwide [1]. With a 5-year survival rate of approximately 3%, long-term survivors of pancreatic cancer are very few [2]. Approximately 50% of patients with pancreatic cancer have distant metastases at diagnosis, and palliative chemotherapy is indicated for these patients, with novel treatments developed in recent years [2]. Regarding available pancreatic cancer treatments, compared to gemcitabine (GEM), both FOLFIRINOX and GEM + nab-paclitaxel prolong overall survival (OS) as first-line chemotherapies [2–4]. In addition, nanoliposomal irinotecan (nal-IRI) with fluorouracil and folinic acid (NFF) reportedly prolongs OS as a second- or later-line chemotherapy [5, 6].

In addition to the lack of appropriate treatment, one possible reason for the poor prognosis of pancreatic cancer is the lack of absolute biomarkers for evaluating prognosis. Six biomarkers are effective for evaluating prognosis: the C-reactive protein (CRP)/albumin ratio (CAR), Glasgow prognostic score, prognostic index, prognostic nutrition index, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio [7–10]. The prognostic value of these factors has been examined based on evaluations at the start or end of chemotherapy. For example, in previous studies, we examined the prognostic significance of the CAR prior to first- or second-line chemotherapy [11, 12]. However, no study has focused on the time-dependent changes in inflammatory markers, such as the CAR. Moreover, data on the effectiveness of such prognostic biomarkers during NFF administration in the clinical setting are insufficient. Nevertheless, research in this regard would be valuable in validating the CAR as a biomarker for pancreatic cancer, thereby improving prognostication. Enhancing the accuracy of prognostication is important to help clinicians estimate survival, recurrence risk, and disease progression. Improved

prognostic biomarkers could also support personalized treatment planning by identifying patients who may benefit from more intensive therapy or closer monitoring. In this milieu, the present study was conducted to verify whether time-dependent changes in the CAR during NFF administration can predict the prognosis of patients with unresectable or recurrent pancreatic cancer (urPC).

Methods

Study design and patients

The present study was a part of an analysis of a prospective cohort from a multicenter observational study in Japan (NAPOLEON-2 study) [13] that involved patients with urPC who received NFF treatment from June 1, 2021 to October 26, 2023 across 17 institutions and were followed up until May 26, 2024. The present study did not set the number of patients based on statistical hypothesis testing but was conducted based on a preliminary survey of NFF administration at the participating institutes instead.

The key eligibility criteria were as follows: patients with Eastern Cooperative Oncology Group performance status of 0–2 who received NFF as a second- or later-line chemotherapy for urPC and were aged ≥ 20 years [14]. The exclusion criteria were as follows: neuroendocrine carcinoma, severe diarrhea, interstitial pneumonia, massive pleural effusion, and concurrent overlapping cancers, except for curable intraepithelial and intramucosal cancers.

The general administration schedule was as follows: nal-IRI (70 mg/m^2) and folinic acid (200 mg/m^2) were intravenously administered, and fluorouracil (2400 mg/m^2) was continuously administered for 46 h on day 1 every 2 weeks. For patients homozygous for UGT1A1*6 or UGT1A1*28 or those heterozygous for UGT1A1*6 and UGT1A1*28, nal-IRI at a starting dose of 50 mg/m^2 was recommended. As this was an observational study, the administration schedule and dosage were left to the discretion of the physician-in-charge.

The institutional review board of each participating institution approved the study protocol (approval no. UMIN000043939). Written informed consent was obtained from all the patients. The present study was conducted in accordance with the principles of the Declaration of Helsinki.

Outcomes

The primary endpoint was the OS. The key secondary endpoints were progression-free survival (PFS) and response rate. OS was defined as the time from NFF initiation to patient death; PFS was defined as the time from NFF initiation to death or progression, whichever occurred earlier. Disease response and progression were assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 [15].

The CAR was calculated by dividing the CRP (mg/dL) by albumin level (g/dL). The cutoff for CAR was 0.54 according to prior publications [7, 11, 12]. The CAR at the start of NFF administration was defined as CAR(1). The minimum CAR value at the start or during NFF administration was defined as CAR(min).

Patients who had received only one cycle of NFF and those with missing data on albumin level or CRP were excluded from the analysis of CAR(min). CAR(min) was equal to CAR(1) when there was no decrease from the baseline.

Statistical analyses

OS was calculated using the Kaplan–Meier method, and the log-rank test was applied to compare survival curves. Hazard ratios (HRs) were estimated using the Cox proportional hazards model with 95% confidence intervals [16]. Statistical significance was set at $p < 0.05$ (two-sided). There were no complements for missing data. A time-dependent receiver operating characteristic (ROC) curve was used to set the cutoff value for CAR(min)/CAR(1) according to median OS (mOS). Landmark analysis was also performed to examine survival using CAR(min)/CAR(1) at 2, 3, and 4 months to reduce immortal time bias [17]. The EZR software was used for statistical analyses [18].

Results

Patient characteristics

One hundred and fifty patients comprised the prospective cohort of the NAPOLEON-2 study. The median follow-up duration was 7.17 (range, 0.63–28.68) months. After excluding one patient with missing data on albumin level before the first course of NFF, 149 patients were included in the analysis for CAR(1). For CAR(min), we excluded six patients who received only one cycle of NFF and four patients with missing data on albumin level; thus, 139 patients were included in the analysis (Figure 1). Patient characteristics are shown in Table 1. In the analysis for CAR(1), there were 25 patients in the CAR(1) ≥ 0.54 group and 124 patients in the CAR(1) < 0.54 group, with a median age of 70 (range, 50–80) and 72 (range, 45–85) years, respectively.

Overall, 137 (91.3%) patients discontinued NFF treatment and 13 (8.7%) continued it. Disease progression (n=118, 78.7%), adverse events (n=10, 6.7%), patient requests (n=4, 2.7%), and other factors (n=5, 3.3%) were the reasons for NFF discontinuation. By the end of the follow-up period, 123 patients died: 122 in the analysis for CAR(1) and 112 in the analysis for CAR(min). The mOS period for confirmed death was 6.5 (range, 0.66–24.70) months.

Analysis of OS based on CAR(1) and CAR(min)

The mOS for patients with CAR(1) < 0.54 (8.98 months; 95% confidence interval [CI], 7.20–9.84) was significantly better than that for patients with CAR(1) ≥ 0.54 (3.42 months; 95% CI, 2.07–6.28) (HR, 0.49; 95% CI, 0.31–0.77; $p < 0.01$) (Figure 2a). Moreover, the mOS for patients with CAR(min) < 0.54 (9.05 months; 95% CI, 7.27–10.20) was significantly better than that for patients with CAR(min) ≥ 0.54 (2.07 months; 95% CI, 1.41–3.32) (HR, 0.06; 95% CI, 0.03–0.13; $p < 0.01$) (Figure 2b).

Temporal change in the CAR during NFF administration

A time-dependent ROC analysis was performed for CAR(min)/CAR(1), and the best cutoff for CAR(min)/CAR(1) was determined to be 0.5 (Online Resource 1). Considering the ease of clinical application, survival analysis based on CAR(min)/CAR(1) was performed using an approximate cutoff value of 0.5. There was a significant difference in the mOS between the CAR(min)/CAR(1) < 0.5 and CAR(min)/CAR(1) ≥ 0.5 groups (10.59 [95% CI, 9.14–14.01] months vs. 6.15 [95% CI, 4.90–7.20] months; HR, 0.33; 95% CI, 0.22–0.51; $p < 0.01$) (Figure 3).

The median duration from the start of NFF administration to CAR(min) was 2.17 (range, 0.43–16.64) months in 90 patients, excluding 49 patients with CAR(1)=CAR(min). As the median PFS of the 139 patients included in the CAR(min) analysis was 4.21 months (95% CI, 2.93–5.00), we set the landmark analysis points at 2, 3, and 4 months after NFF initiation. The OS was clinically better in the CAR(min)/CAR(1) < 0.5 group than in the CAR(min)/CAR(1) ≥ 0.5 group at all landmark points (Figure 4a–4c).

To explore cases with higher CAR(min)/CAR(1) that might includes cases with better prognosis, we compared OS among the following three groups: CAR(min)/CAR(1) < 0.5, CAR(1) ≥ 0.045 and CAR(min)/CAR(1) ≥ 0.5, and CAR(1) < 0.045 and CAR(min)/CAR(1) ≥ 0.5. The cutoff value of 0.045 for CAR(1) was determined based on the median value of CAR(1) < 0.54, and this value indicated a group with remarkably good CAR(1). The OS of the CAR(1) ≥ 0.045 and CAR(min)/CAR(1) ≥ 0.5 group was significantly worse than that of the CAR(1) < 0.045 and CAR(min)/CAR(1) ≥ 0.5 group (HR, 2.11; 95% CI, 1.32–3.38; $p < 0.01$). Moreover, there was a clinically significant difference in the OS between the CAR(min)/CAR(1) < 0.5 and CAR(1) < 0.045 and CAR(min)/CAR(1) ≥ 0.5 groups (HR, 0.47; 95% CI, 0.28–0.76) (Online Resource 2).

Discussion

In the present study, we examined whether temporal changes in the CAR during NFF administration can be useful in predicting the prognosis of patients with urPC. No previous prospective study has shown that a reduction in the CAR is a prognostic biomarker in landmark analysis. To the best of our knowledge, the present study is the first to demonstrate that tracking the temporal changes in the CAR during NFF administration is useful in predicting urPC prognosis.

Most studies have shown the relationship between inflammatory markers and prognosis and their usefulness at the start of treatment, while only a few have evaluated these aspects both before and after treatment [11, 12]. Shirakawa et al. previously compared the significance of inflammatory markers before and after first-line treatment for pancreatic cancer and reported that the CAR was the best determinant of survival prognosis [11]. In addition, the NN-2302 study compared the usefulness of inflammatory markers before and after NFF administration as a second-line treatment and showed a favorable trend in the CAR, supporting the findings of Shirakawa et al. [11, 12]. However, the disease status in the clinical setting is generally not constant owing to the influence of various factors, such as the tumor environment and drug resistance. As such, it is difficult to determine the disease status only

using inflammatory markers before treatment [19–21]. Therefore, we consider it important to evaluate disease status by monitoring inflammatory markers during chemotherapy.

In the present study, the group with CAR(1) < 0.54 had a significantly better OS than the group with CAR(1) ≥ 0.54, prospectively demonstrating the reproducibility of our previous study findings [11, 12]. In addition, the HRs for CAR(1) < 0.54 and CAR(min) < 0.54 were 0.49 and 0.06, respectively, suggesting that CAR(min) has a greater role in predicting prognosis than does CAR(1). These results support the importance of CAR monitoring. Fan et al. [22] categorized the CAR before chemotherapy and after two courses of chemotherapy, and reported that both the CARs were valid biomarkers for OS. However, they did not monitor the temporal changes in the CAR during chemotherapy. In the present study, we demonstrated the clinical significance of CAR(1) and CAR(min), which is meaningful as our findings indicate that CAR(min) during treatment is a predictor of prognosis.

We identified a significant difference in OS between the CAR(min)/CAR(1) ≥ 0.5 and CAR(min)/CAR(1) < 0.5 groups (Fig. 3). CAR(min) is determined at the end of NFF administration, and CAR(min)/CAR(1) < 0.5 is reached the moment a patient's CAR is less than half of their CAR(1). In such cases, we may consider that the patient shows a good prognosis even during NFF administration, thereby providing useful information for both patients and physicians in daily practice. The expression of C-reactive protein, a component of the CAR, is induced by interleukin 6; the CRP level increases with tumor progression, and a lower CRP level indicates a better prognosis [23–25]. The other CAR component, albumin, is an indicator of nutritional status, particularly in patients with pancreatic cancer, who are sometimes undernourished at initial diagnosis; lower albumin levels shorten OS [26–28]. Therefore, decreased CAR might be associated with favorable OS, and it may further indicate an improvement in tumor inflammation or nutritional status.

In the present study, patients with significantly lower CAR(1) had high CAR(min)/CAR(1), indicating that patients with higher CAR(min)/CAR(1) may partially include patients with better prognosis. Therefore, we performed a sub-analysis and observed clinically better OS in the CAR(min)/CAR(1) < 0.5 group, followed by the CAR(1) < 0.045 and CAR(min)/CAR(1) ≥ 0.5 and CAR(1) > 0.045 and CAR(min)/CAR(1) ≥ 0.5 groups. This finding reconfirmed the clinical utility of CAR(min)/CAR(1) < 0.5 and indicated that the prognosis of patients with CAR(1) < 0.045 is not poor, even in those with CAR(min)/CAR(1) ≥ 0.5.

We further addressed the possibility that CAR(min) may be influenced by the clinical course of NFF administration or tumor status by conducting a landmark analysis. The landmark analysis is advantageous in terms of reducing immortal bias by removing events prior to the landmark point, allowing us to perform a sensitivity analysis using multiple landmark points [29–31]. However, it also has limitations, such as reduced power owing to the relatively small cohort size and inconsistency in hazard ratios at multiple landmark points [29, 20]. In the landmark analysis, CAR(min)/CAR(1) < 0.5 was associated with significantly better OS at every landmark point with no discrepancy in HRs. Less than one-third of the patients were included in the analysis during the period that we defined as landmark points, and this may not have reduced the power of the analysis to show clinical differences. Taken

together, we consider that temporal monitoring of the CAR is meaningful and that a decrease in CAR value is clinically useful to predict better prognosis in the real world.

The present study has some limitations. First, the number of patients with CAR(1) ≥ 0.54 or CAR(min) ≥ 0.54 was not large, making it difficult to conduct further analyses, such as multivariate analysis. However, we were able to identify a patient population showing particularly poor prognosis with CAR(min) ≥ 0.54. Second, we set an approximate cutoff of 0.5 for CAR(min)/CAR(1) in accordance with the time-dependent ROC curve analysis, and further verification is required to determine the appropriate cutoff. However, the CAR(min)/CAR(1) cutoff of 0.5 can be easily applied in daily practice. Furthermore, albumin and CRP levels can usually be measured during each course of chemotherapy, and the CAR is advantageous in terms of being easier and faster to assess than imaging. Finally, as we validated the temporal decrease in CAR as a prognostic biomarker, we did not have any data on worsening CAR or other inflammatory markers. However, it is meaningful to repeatedly demonstrate the usefulness of the CAR, as observed in our previous studies [11, 12].

Our results show that CAR(min) is a good prognostic biomarker that may be superior to CAR(1); therefore, we suggest that it is valuable to monitor the CAR trends over time. Further validation of the appropriate cutoffs for CAR(min) and CAR(min)/CAR(1) is required; however, the cutoff of 0.5 for CAR(min)/CAR(1) can be easily applied in actual medical practice. Overall, by showing that temporal changes in CAR during treatment correlate with OS, this study suggests that continuous monitoring of this marker can provide valuable insights into disease progression and treatment response. Incorporating CAR monitoring into clinical practice could help physicians make more informed decisions about therapy adjustments and patient management.

Declarations

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest

Otsu S declares speaker engagement with Ono Pharmaceutical, Daiichi-Sankyo Company, Eli Lilly Japan K.K., Bristol-Myers Squibb Company, and Taiho Pharmaceutical. Nishikawa K declares speaker engagement with Teijin Pharma, Takeda Pharmaceutical Company, Daiichi-Sankyo Company, Novartis Pharma, Bristol-Myers Squibb Company, and Nihon Service. The remaining authors have no competing interests or financial disclosures to declare.

Research involving Human Participants

Ethics approval

The institutional review board of each participating institution approved the study protocol (approval no. UMIN000043939). The present study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed consent

Consent to participate

Written informed consent was obtained from all the patients included in this study.

Consent to publish

Not applicable

Data availability statement

All data generated or analyzed in the present study are stored in a secure research database. Although not publicly available, they are available through the corresponding author on reasonable request.

Author Contributions

Conceptualization: Tomonori Araki, Amane Jubashi, Kohei Hayashi, Takuya Honda, Hisamitsu Miyaaki, Tsuyoshi Shirakawa, Mototsugu Shimokawa, Taiga Otsuka, Toshihiko Mizuta, Kenji Mitsugi. Formal analysis and investigation: Tomonori Araki, Taiga Otsuka, Mototsugu Shimokawa, Junichi Nakazawa, Hozumi Shimokawa, Yudai Shinohara, Futa Koga, Noriko Oza, Hisanobu Oda, Shigeyuki Takeshita, Shiho Arima, Koshiro Toyodome, Ryusuke Shibata, Shuji Arita, Yasunori Kawaguchi, Kazuo Nishikawa, Satoshi Otsu, Hiroki Taguchi, Kenichi Jikuya, Tatsunori Sakai, Yujiro Ueda, Takahiro Sakae, Norimasa Araki, Hironori Sawase, Yasushi Ide, Machiko Kawahira, Kenta Nio, Tsuyoshi Shirakawa, Toshihiko Mizuta, Kenji Mitsugi. Writing - original draft preparation: Tomonori Araki, Tsuyoshi Shirakawa, Taiga Otsuka. Writing - review and editing: Tomonori Araki, Taiga Otsuka, Mototsugu Shimokawa, Amane Jubashi, Kohei Hayashi, Takuya Honda, Hisamitsu Miyaaki, Tsuyoshi Shirakawa, Toshihiko Mizuta, Kenji Mitsugi. Supervision: Tsuyoshi Shirakawa, Taiga Otsuka, Mototsugu Shimokawa, Toshihiko Mizuta, Kenji Mitsugi

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Table

Table 1 Patient characteristics

	CAR(1) ≥ 0.54 (n = 25)	CAR(1) < 0.54 (n = 124)
Age, median (range), years	70 (50–80)	72 (45–85)
Sex, female	6 (24%)	63 (51%)
ECOG performance status		
0	2 (8%)	43 (35%)
1	19 (76%)	74 (60%)
≥2	4 (16%)	7 (6%)
History of malignancy	8 (32%)	21 (17%)
Family history of malignancy	14 (56%)	50 (40%)
Previous tumor resection	4 (16%)	37 (30%)
Pancreatic tumor location		
Head	11 (44%)	51 (41%)
Body	10 (40%)	39 (31%)
Tail	4 (16%)	34 (27%)
Histological subtype		
Adenocarcinoma	22 (88%)	109 (88%)
Others	1 (4%)	5 (4%)
Unknown	2 (8%)	9 (7%)
Stage		
Locally advanced	3 (12%)	13 (10%)
Metastatic	18 (72%)	75 (60%)
Recurrence	4 (16%)	36 (29%)
Liver metastasis	18 (72%)	58 (47%)
Lung metastasis	7 (28%)	35 (28%)
Peritoneal metastasis	5 (20%)	41 (33%)
Ascites		
Abdominal	3 (12%)	10 (8%)
Pelvic	7 (28%)	22 (18%)
Line of NFF		

Second	16 (64%)	71 (57%)
Third	8 (32%)	44 (35%)
Fourth or higher	1 (4%)	9 (7%)
Previous treatment		
Therapy containing GEM	25 (100%)	124 (100%)
Therapy containing IRI	3 (12%)	16 (13%)
5-FU course, median (range)	3 (1–33)	7 (1–44)
nal-IRI course, median (range)	3 (1–33)	7 (1–44)
UGT1A1 *6/*28		
Wild	12 (48%)	57 (46%)
Single hetero	9 (36%)	49 (40%)
Double hetero	1 (4%)	2 (2%)
Homo	1 (4%)	5 (4%)
Unknown	2 (8%)	11 (9%)

Data are presented as n (%), unless indicated otherwise.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NFF, nanoliposomal irinotecan, 5-fluorouracil, and folinic acid; GEM, gemcitabine; 5-FU, 5-fluorouracil; IRI, irinotecan; nal-IRI, nanoliposomal irinotecan; CAR (1), CRP-albumin ratio at the start of NFF; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1

Figures

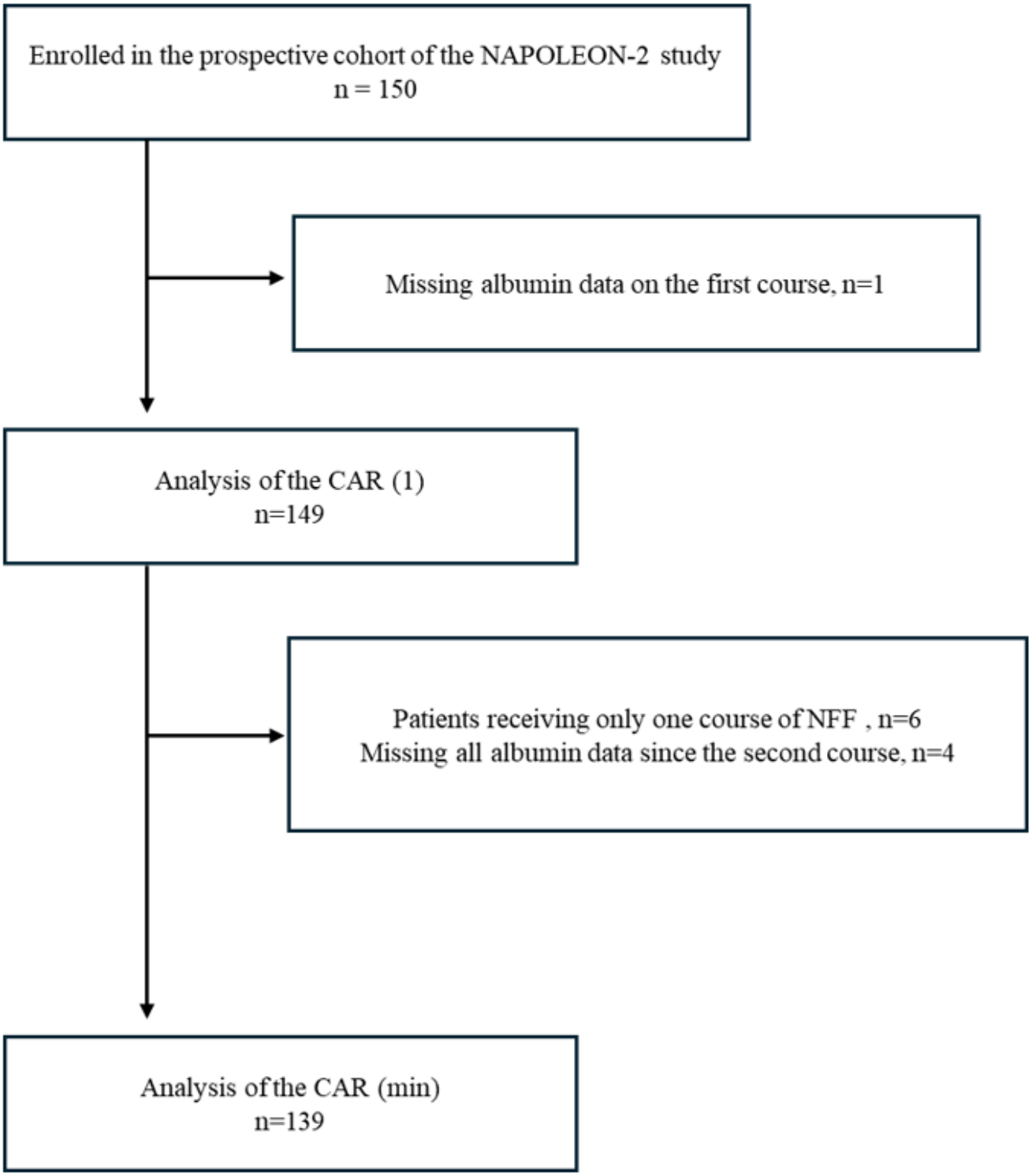

Figure 1

Flow diagram of patient inclusion or exclusion

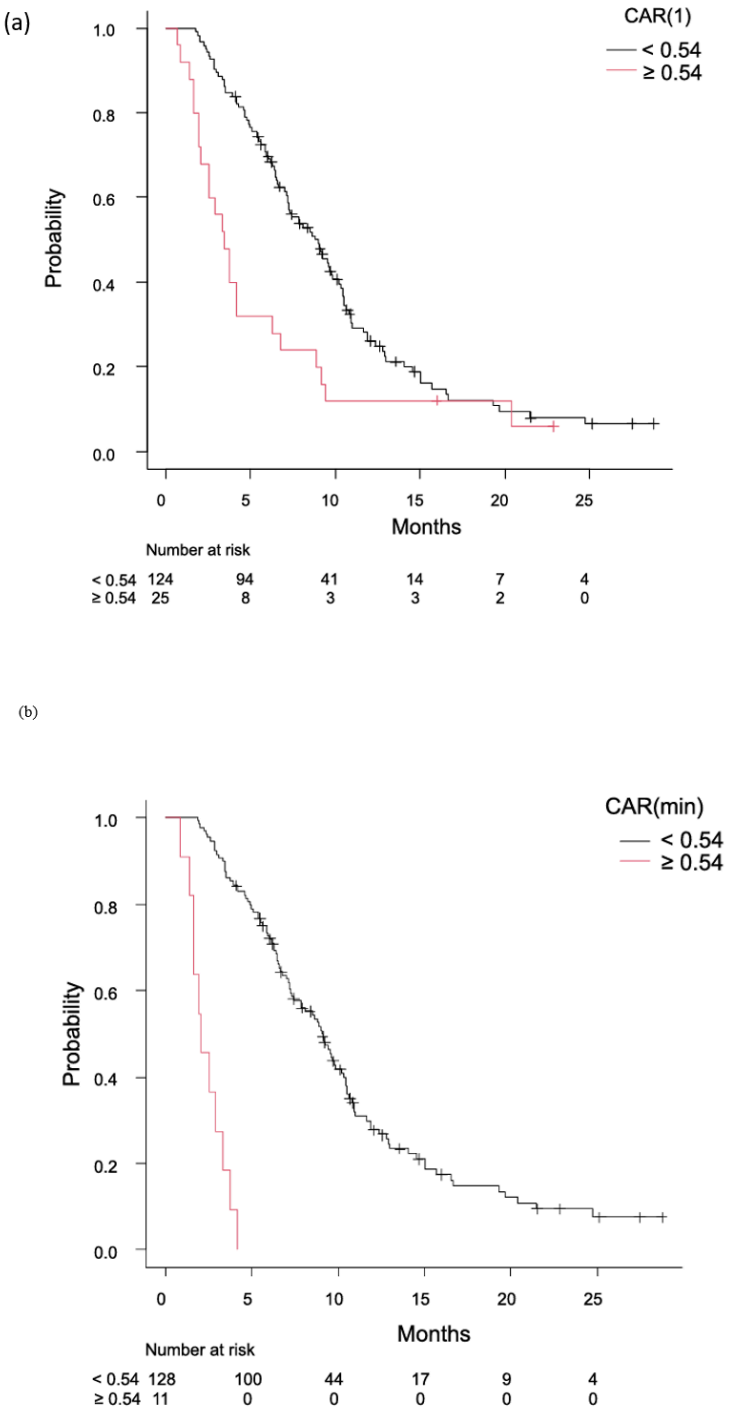

Figure 2

Kaplan–Meier overall survivalcurves of NFF at initiation and time of minimum CAR

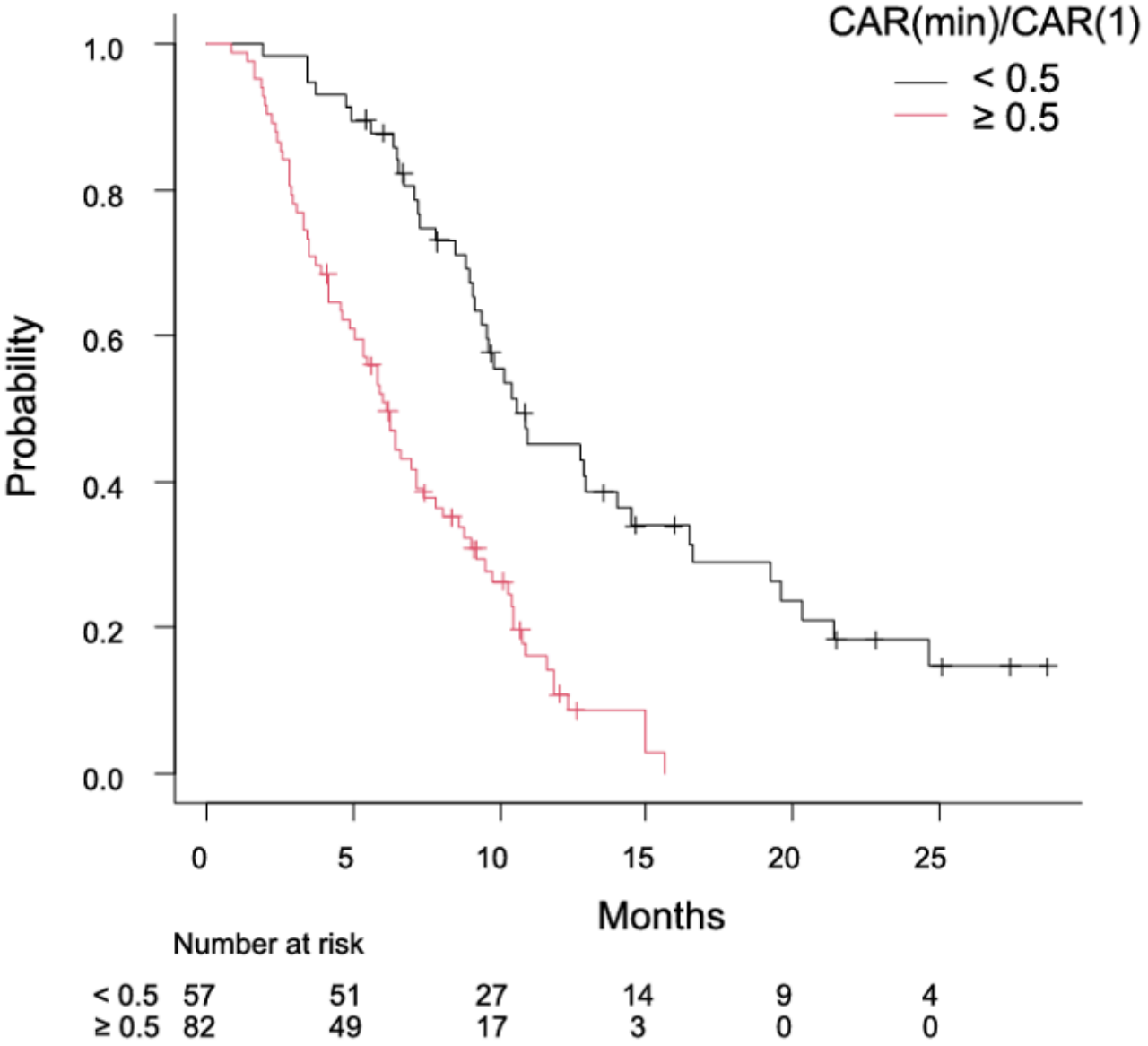

Figure 3

Kaplan–Meier overall survival curve stratified based on CAR(min)/CAR(1)

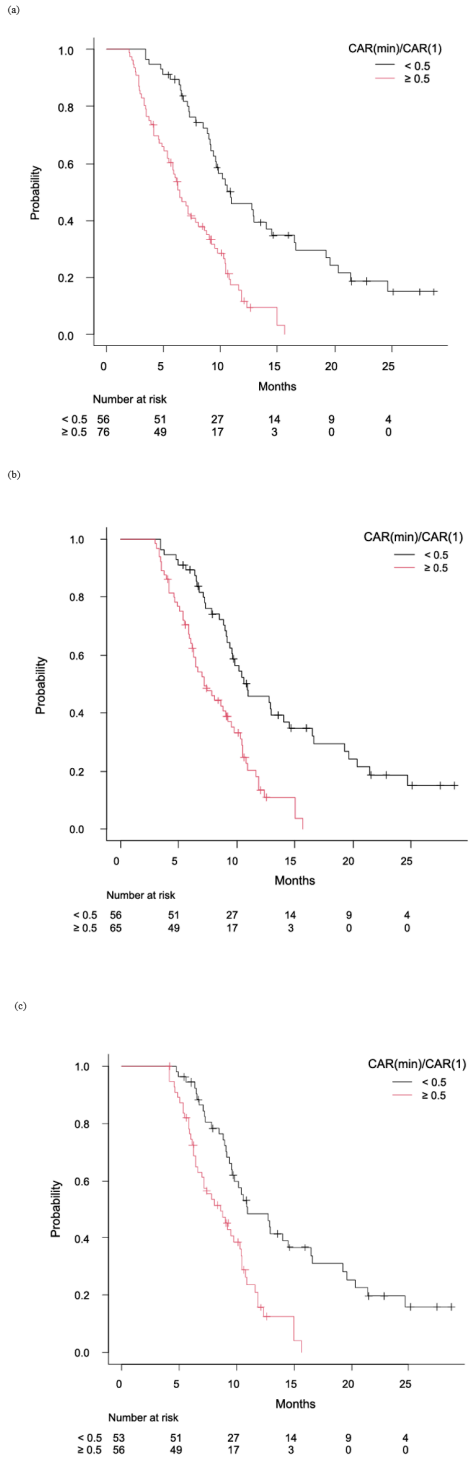

Figure 4

Kaplan–Meier overall survival curves stratified based on CAR(min)/CAR(1) with landmark analysis

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplFig1and2.docx