Liver fibrosis indices predict length of hospitalization and mortality in SARS-CoV-2 infected patients

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Research Article

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Abstract

Background: The ongoing COVID-19 pandemic has challenged health systems under multiple aspects. The deep understanding of risk and prognostic factors for this disease may help not only in reducing severity and mortality but also in targeting therapies considering patients' individual features. Liver Fibrosis is considered a complication in Non-alcoholic Fatty Liver Disease (NAFLD), being a feature of steatohepatitis (NASH), and it had already been related to an increased risk for a wide range of diseases.

Methods: Here, we analysed a sample of 271 patients with moderate-to-severe SARS-CoV-2-related respiratory failure, hospitalized in a sub-intensive care Unit, with the aim of unveiling if any condition may predict their prognosis and mortality.

Results: We found that non-invasive scores of liver fibrosis such as AAR, FIB-4 and mFIB-4, Forns, and AARPRI strongly predict not only in-hospital mortality but also the length of hospitalization and the eventual admission to intensive care units.

Conclusions: Thus, pre-existing liver metabolic disease is a net predictor of poor prognosis in SARS-CoV-2 infected patients admitted to Sub-Intensive Care Unit.

Introduction

SARS-CoV-2 enters the peripheral blood from the lungs and spread into cells that express angiotensin-converting enzyme 2 (ACE-2), that represents the cognate receptor of the envelope Spike protein of SARS-CoV-2. Then, the intracellular lifecycle of virus starts. The infected host cells trigger an immune response with the recruitment of T lymphocytes, monocytes, and neutrophils [1]. In severe COVID-19, the immune system's overactivation results in a "cytokine storm" characterized by the release into the circulation of high levels of some cytokines, especially Interleukine-6 (IL-6) and Tumour Necrosis Factor- α (TNF-α), causing a local and systemic inflammatory response [2]. In addition to IL-6 and TNF-α, the binding of SARS-CoV-2 to the Toll-Like Receptor (TLR) leads to the release of IL-1β, which mediates lung inflammation, that can evolve into fibrosis, responsible for the well-known severe pulmonary manifestations [3].

Similarly, inflammation and releasing of a plethora of cytokines and adipocytes specific hormones are linked to an excessive fat accumulation, specifically visceral adiposopathy, representing a risk factor for cardiovascular, metabolic and chronic obesity-related diseases, including cancer [4].

On one hand, patients with increased abdominal obesity show decreased diaphragmatic excursion that compromises pulmonary function in supine position, making ventilation more difficult [5]. Anyway, the impact of obesity on respiratory diseases is complex and goes beyond the obvious physical and mechanical effects of weight gain and its associated metabolic and inflammatory disorders. Elevated levels of interleukins IL-6, IL-8, TNF-α, C-Reactive Protein (CRP), leptin, and lower level of adiponectin may represent the pathogenetic link between obesity-induced hypoxemia and related respiratory disorders [6].

Furthermore, obesity is strongly linked with respiratory symptoms and diseases, including exertional dyspnea, obstructive sleep apnea syndrome (OSAS), obesity hypoventilation syndrome (OHS), chronic obstructive pulmonary disease (COPD), asthma, pulmonary embolism, and aspiration pneumonia [7].

On the other hand, obesity and its related conditions, especially type 2 diabetes and hypertriglyceridemia, are major contributors to the current epidemic of Non-Alcoholic Fatty Liver Disease (NAFLD) [8] Non-Alcoholic Steatohepatitis (NASH) in which the accumulation of fat in hepatocytes causes inflammation, cell death, and fibrous scarring resulting in disruption of normal hepatic architecture and hepatic dysfunction. Since chronic liver injury results in repeated tissue damage that leads to an imbalance between extracellular matrix production and dissolution, steatohepatitis is associated with liver fibrosis. Fibrosis does not cause symptoms but can lead to portal hypertension, in which scar tissue alters hepatic portal flow, and cirrhosis. To date, metabolic causes, associated with chronic insult leading to a picture of liver fibrosis, are much more common. Hepatic fibrosis is the most important factor of mortality in NAFLD, since the risk of death from hepatitis increases exponentially with an increasing level of fibrosis [9]. Although liver biopsy appears to be the gold standard for staging liver fibrosis, alternative methods of evaluation are increasingly validated and used, especially because they are non-invasive, clinical, and cheap, including several variables, such as age, anthropometric data, and laboratory values. Consequently, non-invasive clinical assessment systems have gained validity as first-line tools in patients with hepatic fibrosis. Moreover, in NAFLD patients, those non-invasive scoring systems are good predictors of morbidity and mortality and had an additive value in predicting the development of hepatic and extra-hepatic cancers [10].

The aim of this study has been the one to understand whether metabolic patients have an increased risk of mortality from COVID-19 and which of the parameters assessing the metabolic status of patients have a greater ability in identifying patients at risk for poorer prognosis.

Therefore, the initial phase of the study focused on analysing the bio-humoral and haemato-chemical parameters and liver fibrosis scores to determine metabolic abnormalities in the study population. In a second phase, attention was focused on identifying whether there were statistically significant differences between patients who died during hospitalization and patients discharged to home or moved to Intensive Care Unit (ICU). We analysed and correlated the various markers, identifying the most representative ones in predicting mortality and prognosis. Finally, we focused on studying which of these parameters showed a correlation with the length of hospitalization in our Unit.

Materials And Methods

Study Participants

Patients' recruitments, clinical and biochemical analysis were registered consecutively in the electronic health register of Medicina Sub-Intensiva Unit of Presidio Maxi-Emergenze (MSI-PME) at Teaching Hospital Policlinico di Bari, Italy from April 2021 to April 2022. Admitted patients presented respiratory

failure due to SARS-CoV-2 infection and requiring oxygen therapy up to noninvasive ventilation. A total of 443 patients with 18 or more years were enrolled in this study at the beginning, among which 148 were excluded since fundamental biochemical data such as AST, ALT, GGT, or blood count were lacking.

Patients with previous viral hepatitis, cirrhosis, benign liver tumours (BLT), primary liver cancer (PLC) or hepatic metastasis at baseline (n = 13) and who admitted POTUS (n = 11) were excluded from the study.

In the end, statistical analysis was performed on a total population of 271 patients (149 males, 122 females). The flowchart of the study population is shown in Fig. 1.

The study was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria Policlinico di Bari (Bari, Italy) in accordance with the requirements of the Declaration of Helsinki. Written informed consent for the use of clinical data was obtained from all participants in the study.

Baseline Evaluation And Biochemical Measurements

All participants underwent a detailed anamnesis and physical examination at the admission. Unfortunately, precise anthropometric assessment at time 0 was not performed for all patients due to their critical illness at the admission.

Morning blood samples were obtained after 12 hours of fasting from the antecubital veins of patients on the first day after the admission to our Unit. After blood clotting and centrifugation, serum was processed for analysis of biochemical markers of glucose and lipid metabolism. Liver, renal, thyroid and inflammatory markers were as well studied following standardized biochemical procedures. All biochemical measurements were centralized and performed in the ISO 9001 certified laboratories of the University Hospital of Bari. Specifically, a complete blood count with determination of leukocyte's subpopulation was performed. Measurements of total and High-Density Lipoprotein cholesterol (HDL-c), fasting plasma glucose (FPG), triglycerides (TG) were obtained through enzymatic colorimetric assay (Siemens, Erlangen, Germany). CPR via nephelometry (Siemens, Erlangen, Germany). Low-density Lipoprotein cholesterol (LDL-c) level was obtained using the Friedewald formula and Neutrophil to Lymphocyte Ratio (NLR) and Monocyte to HDL-c ratio (MHR) were calculated manually.

Statistical Analysis

Descriptive statistical analyses of study sample were performed, and their results were expressed as mean ± standard error of the mean (SEM) and frequencies (%), depending on the nature of variables. Comparisons of socio-demographic and clinical variables between two groups were conducted with the t-test (for continuous variables) and the Pearson $\chi 2$ test (for categorical variables). Analysis between more than two groups were performed through one-way analysis of variance (ANOVA) followed, where required, by Bonferroni post-hoc test. The correlation between continuous variables was also analysed and estimated using Pearson's Correlation Coefficient (r). P-values lower than 0.05 were considered

significant. All analyses were performed using GraphPad Prism, version 9.1.0 (GraphPad Software; San Diego, USA).

Liver Fibrosis Non-Invasive Scores

The ratio of AST to ALT (AAR), which is typically less than 1, can rise to greater values as fibrosis and cirrhosis develop. According to a study by Giboney et al., 87 percent of patients with an AAR of 1.3 or less had NASH (87 percent sensitivity, 84 percent specificity). The severity of NASH as measured by the degree of fibrosis increased, as did the AAR. The mean ratio of 1.4 was found in patients with cirrhosis related to NASH. Wilson's disease can cause the AAR to exceed 4. In summary, certain AARs are suggestive of certain conditions. Consequently, since there is significant overlap between AAR in different conditions, and the exact mechanism of AAR alteration in progression of liver disease is unclear, its accuracy in predicting the degree of fibrosis and the presence of cirrhosis is controversial and this ratio cannot be relied on exclusively when making a diagnosis [11].

FIB-4 index is a non-invasive score to assess liver fibrosis in outpatient settings. The index is considered to be accurate, non-invasive, and easily available, and may be useful in evaluating patients with Hepatitis-C Virus (HCV), NAFLD, and other liver complications [12].

The modified fibrosis-4 (mFIB-4) index was elaborated as an instrument to assess the stage of liver fibrosis in patients with chronic hepatitis B (CHB) or C (CHC). However, it is used for the detection of advanced liver fibrosis in all patients with chronic liver disease [13].

Forns index is based on the assessment of four routine-parameters (age, platelets count, cholesterol, and GGT). The most important study to evaluate its diagnostic accuracy considered a cohort of 250 patients with CHC. The Forns index is able to exclude the presence of severe fibrosis with a Negative Predictive Value of 96% and to identify the presence of severe fibrosis with a Positive Predictive Value of only 66%. It is therefore a useful test in identifying patients with minimal fibrosis but it has limited value in identifying patients with more advanced liver disease [14].

APRI score (AST to Platelet Ratio Index) is a non-invasive index for the assessment of liver fibrosis in patients with viral hepatitis, and represents an alternative to liver biopsy in the follow-up of patients with hepatitis C and liver cirrhosis in outpatient setting. In a meta-analysis of 40 studies, it was concluded that an APRI score above 1.0 presents a sensitivity of 76% and a specificity of 72% for predicting cirrhosis. An APRI score above 0.7 presents a sensitivity of 77% and a specificity of 72% for predicting significant liver fibrosis [15]. It is likely that APRI alone is not sensitive enough to rule out significant disease. Some evidence suggests that the use of multiple indices in combination (such as APRI plus FibroTest) or an algorithmic approach could result in greater diagnostic accuracy than using APRI alone [16].

AARPRI (AAR to Platelet Ratio Index) represents another important non-invasive score for the evaluation of hepatic fibrosis. In particular, it can be considered as one of the most reliable scores in the diagnosis of advanced stages of liver fibrosis. Moreover, AARPRI had also been proposed as a predictor for chronic liver disease-associated complications [17],[18].

All formulas used for calculating non-invasive liver fibrosis scores are summarised in Supplementary Table 1.

Results

The median age of our 271 patients was 69.7 years. Mean length of the stay in our Unit was 13.18 days. 38 patients (19 males and 19 females) died during the hospitalization in our Unit, while 233 (130 males and 103 females) were still alive when they moved away from our Unit. Of them, 208 patients (117 males and 91 females) were discharged, while 25 patients (13 males and 12 females) were transferred to ICU for the worsening of their clinical conditions.

As shown in Table 1, non-survivor patients were significantly older ($p < 0.001$) and exhibited increased lymphocytopenia ($p < 0.05$) and glycemia ($p < 0.001$) at the admission. Surprisingly, no significant differences were found for inflammation markers (WBC, CRP, ESR, Ferritin) except for Procalcitonin ($p < 0.05$). With regard to lipid assessment, total cholesterol and LDL-cholesterol (LDL-c) were significantly lower in non-survivor group ($p < 0.05$) while no statistical differences were found for AST, GGT, Total Bilirubin, and NT-proBNP. Myocitolysis parameters as LDH ($p < 0.001$), CPK ($p = NS$), Myoglobin ($p < 0.05$), and hs-Troponin ($p < 0.05$) were all increased in the second group.

Table 1
Baseline characterization of the study population.

Clinical variable	Survivors	Non survivors	p-value
n (M:F)	233 (130:103)	38 (19:19)	-
Age (years)	67.88 ± 1.027	82.68 ± 1.697	< 0.001
Hemoglobin (g/dl)	12.4 ± 0.163	11.9 ± 0.374	NS
WBC (10^3/µl)	8.46 ± 0.306	9.48 ± 0.798	NS
Monocytes (%)	6.35 ± 0.212	4.39 ± 0.445	< 0.001
Lymphocytes (%)	16.4 ± 0.75	9.5 ± 1.25	< 0.001
Neutrophils (%)	76.1 ± 0.875	85.3 ± 1.45	< 0.001
NLR	7.83 ± 0.539	16.7 ± 2.66	< 0.001
Platelet count (10^6/µl)	249 ± 7.98	217 ± 17.1	NS
Creatinine (mg/dl)	1.51 ± 0.262	1.5 ± 0.213	NS
Urea (mg/dl)	58.3 ± 3.01	97.8 ± 13.2	< 0.001
Glucose (mg/dl)	113 ± 3.3	137 ± 12	< 0.05
Total Cholesterol (mg/dl)	156 ± 4.06	133 ± 6.1	< 0.05
HDL-c (mg/dl)	39 ± 1.48	34.7 ± 2.67	NS
LDL-c (mg/dl)	86.3 ± 3.32	68.6 ± 5.41	< 0.05
NON HDL-c (mg/dl)	116 ± 4.31	98.6 ± 5.92	NS
TG (mg/dl)	146 ± 7.54	153 ± 13.1	NS
MHR	0.0148 ± 0.00142	0.0135 ± 0.00202	NS
AST (U/I)	38.8 ± 2.06	37.2 ± 3.32	NS
ALT (U/I)	43.7 ± 3	27.9 ± 2.52	< 0.05
GGT (U/I)	68.1 ± 5.35	61.1 ± 14.5	NS
Total Bilirubin (mg/dl)	0.684 ± 0.0502	0.724 ± 0.0896	NS

Data are presented as mean ± SEM (standard error of the mean). Abbreviations: White Blood Cells, WBC; Neutrophil to Lymphocyte Ratio, NLR; High-density Lipoprotein Cholesterol, HDL-c; Low-density Lipoprotein Cholesterol, LDL-c; Triglycerides, TG; Monocytes to HDL-C Ratio, MHR; Aspartate Transaminase, AST; Alanine Transaminase, ALT; high-sensitivity C Reactive Protein, Hs-CRP; Erythrocyte Sedimentation Rate, ESR; Lactate dehydrogenase, LDH; Creatine phosphokinase, CPK; high sensitivity Troponin, hs-troponin; N-terminal prohormone of brain natriuretic peptide, NT-proBNP; thyrotropin, TSH; tri-iodothyronine, FT3; thyroxine, FT4; AST to ALT ratio, AAR; fibrosis 4 index, FIB-4; modified FIB-4, mFIB-4; AST to Platelet Ratio Index, APRI; AAR to Platelet ratio, AARPRI.

Clinical variable	Survivors	Non survivors	p-value
Ferritin (ng/ml)	709 ± 62.2	712 ± 102	NS
Procalcitonin (ng/ml)	0.469 ± 0.116	3.05 ± 2.3	< 0.05
hs-CRP (mg/l)	68.2 ± 7.39	98.4 ± 10.9	NS
ESR (mm/h)	65.4 ± 3.27	61.9 ± 9.56	NS
LDH (mU/ml)	303 ± 9.14	407 ± 29	< 0.001
CPK (U/L)	163 ± 32.8	198 ± 59.1	NS
Myoglobin (µg/l)	169 ± 19.4	535 ± 316	< 0.05
hs-Troponin (ng/l)	95.9 ± 29.9	574 ± 384	< 0.05
NT-proBNP (pg/ml)	3562 ± 932	6449 ± 1531	NS
TSH (mUI/L)	1.84 ± 0.355	1.18 ± 0.362	NS
FT3 (pg/ml)	1.63 ± 0.0559	1.19 ± 0.105	< 0.05
FT4 (ng/dl)	1.22 ± 0.0252	1.22 ± 0.0625	NS
AAR	1.1 ± 0.0397	1.55 ± 0.151	< 0.001
FIB-4	2.34 ± 0.183	3.6 ± 0.54	< 0.05
mFIB-4	4.3 ± 0.336	7.4 ± 1	< 0.05
FORNS	7.98 ± 0.146	8.95 ± 0.294	< 0.05
APRI	0.662 ± 0.0543	0.756 ± 0.148	NS
AARPRI	0.915 ± 0.0683	1.36 ± 0.188	< 0.05

Data are presented as mean ± SEM (standard error of the mean). Abbreviations: White Blood Cells, WBC; Neutrophil to Lymphocyte Ratio, NLR; High-density Lipoprotein Cholesterol, HDL-c; Low-density Lipoprotein Cholesterol, LDL-c; Triglycerides, TG; Monocytes to HDL-C Ratio, MHR; Aspartate Transaminase, AST; Alanine Transaminase, ALT; high-sensitivity C Reactive Protein, Hs-CRP; Erythrocyte Sedimentation Rate, ESR; Lactate dehydrogenase, LDH; Creatine phosphokinase, CPK; high sensitivity Troponin, hs-troponin; N-terminal prohormone of brain natriuretic peptide, NT-proBNP; thyrotropin, TSH; tri-iodothyronine, FT3; thyroxine, FT4; AST to ALT ratio, AAR; fibrosis 4 index, FIB-4; modified FIB-4, mFIB-4; AST to Platelet Ratio Index, APRI; AAR to Platelet ratio, AARPRI.

Considering liver fibrosis non-invasive indices, non survivor patients presented significantly increased AAR ($p < 0.001$), FIB-4, ($p < 0.05$), mFIB-4 ($p < 0.05$), Forns ($p < 0.05$), AARPRI ($p < 0.05$), but no significative difference for APRI (Fig. 2).

To better understand if these scores might predict not only the mortality but also the evolution of critical disease and the prognosis, we then performed one-way ANOVA test dividing our population in three groups according to their final outcomes, that is to say if they were discharged after clinical resolution,

moved to ICU because of the worsening of their conditions, or died during hospitalization. The comparison was significantly different for AAR ($p < 0.001$), FIB-4 ($p < 0.05$), mFIB-4 ($p < 0.05$), Forns ($p < 0.01$), and AARPRI ($p < 0.05$), but not for APRI (Fig. 3). APRI only showed a statistically significant difference when compared by T-student test between ICU-admitted and survivor patients (Fig. 3e, $p < 0.05$). Multiple comparisons also showed that only AAR (Fig. 3a) was significantly higher in non-survivors versus either discharged ($p < 0.001$) or ICU-admitted ($p < 0.05$) patients, whereas other comparisons did not reveal any difference between these two groups.

Thus, assuming that the prognosis correlates with the length of the stay, we tried to deepen the correlation between Liver Fibrosis Indices and the days of hospitalization in MSI-PME, finding that all them showed significant correlations (Fig. 4a-4b-4c-4d-4f, $p < 0.05$), apart from APRI (Fig. 4e).

Furthermore, we found that this association remained when we performed the same analysis only in patients who were discharged, excluding those who succumbed or got worse (Fig. 5, $p < 0.05$).

Discussion

In this study, we show that non-invasive scores of liver fibrosis predict mortality and clinical outcomes in COVID-19 patients, and also correlate with the length of the hospitalization.

Similarly, some previous studies found that liver fibrosis was independently associated with mortality, independently of demographic characteristics of patients [19] and particularly, the simple FIB-4 scoring system might predict COVID-19-related mortality, this connection being likely mediated by SARS-CoV-2-associated damage and monocyte associated cytokines [15]. Also AAR had already been associated with increased mortality in hospitalized patients [15]. Concerning the FORNS-index, higher values in non survivors were found by Crisan et al [20]. Similarly to our findings, APRI score failed to predict COVID-19 mortality probably because it does not consider age, that is instead a proven risk factor for poorer prognosis [21]. On the other hand, in our study AARPRI, which also does not consider age, predicts mortality.

We then also studied the possibility that these scores may correlate with more severe clinical outcomes. Thereby, we speculated that prognosis and severity of the disease may be estimated by the need for oro-tracheal intubation (i.e., in our clinical setting, ICU admission) and the length of hospitalization, that surely increases due to pre-existing comorbidity and COVID-19 related-complications [22].

To the best of our knowledge, only few studies had proposed liver fibrosis non-invasive scores, assessed prior to acute COVID-19 illness, to the risk of more severe disease [15], increased odds of hospitalization [23], and orotracheal intubation [19].

Actually, in the setting of acute COVID-19 illness, Metabolic Syndrome and its hepatic features, namely NAFLD and NASH that represent an ongoing pro-inflammatory state, might exacerbate the virus-induced cytokine storm, possibly through hepatic release of pro-inflammatory cytokines, being responsible for

worse prognosis. Besides, in up to 20% of cirrhotic patients admitted in critical care units, respiratory viruses are usually detected and pneumonia is one of the most common infections in patients with advanced liver fibrosis [24]. A more pronounced baseline systemic inflammation profile in patients with liver fibrosis influences different organs and systems and, when SARS-CoV-2 is added, the interaction triggers further inflammatory and immune responses, promoting higher inflammation [25]. Consequently, poorer outcomes in patients with COVID-19 and metabolic disorders might be a result of an “acute on chronic inflammation” process [19].

Furthermore, adipose tissue may serve as a reservoir for SARS-CoV-2 owing to its high level of expression of ACE-2 [26], since although it is detected in lung, its expression is rather lower than extrapulmonary tissues [2]. For instance, ACE-2 is abundantly expressed within the human intestinal tracts, specifically the brush border of intestinal enterocytes along the entire gastrointestinal tract [27], [28], [29]. Not surprisingly, symptoms such as diarrhoea, nausea and/or vomiting, anorexia, and abdominal pain are seen in up to 1 in 5 patients with COVID-19 infection [1] and SARS-CoV-2 RNA has been detected also in faeces, even after respiratory symptoms subsided [30]. Also, hepatic invasion by SARS-CoV-2 may be possible via constitutively expressed ACE-2, mainly on cholangiocytes and, to a lesser extent, hepatocytes. Thus, it has been hypothesised that SARS-CoV-2 induces liver damage primarily in biliary tract, with secondary injury and compensatory proliferation of hepatocytes [31]. Microscopically, pathological features of COVID-19 in the liver include moderate macro vesicular steatosis, mild lobular and portal (mainly lymphocytic) infiltration, patchy hepatic necrosis, and both periportal and centrilobular sinusoidal dilatation [32]. This may lead to that elevation of transaminases usually detected in patients with COVID-19 [31] that may also explain why fibrosis non-invasive indexes are increased. Consequently, even though nowadays severe evidences support the rule of non-invasive liver fibrosis scores in predicting mortality, it still remains unclear if liver fibrosis represents a factor affecting prognosis or an early signature of SARS-CoV-2 infection.

In conclusion, we evaluated for the first time the predictive power of several liver fibrosis scores such as AAR, FIB-4, mFIB-4, Forns index, and AARPRI for mortality and ICU admission in SARS-CoV-2 infected patients. We found that non-invasive scores of liver fibrosis such as AAR, FIB-4 and mFIB-4, Forns, and AARPRI strongly predict not only in-hospital mortality but also the length of hospitalization and the eventual admission to intensive care units. Thus, pre-existing liver metabolic disease is a net predictor of poor prognosis in SARS-CoV-2 infected patients admitted to Sub-Intensive Care Unit.

Declarations

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Gianfranco Inglese, Nicola Susca, Lucrezia dell'Olio, Francesca Falcone, Mariapaola Castaldo, Carlo De Matteis, Antonio Moschetta declare that they have no conflict of interest.

Informed Consent Statement: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

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Figures

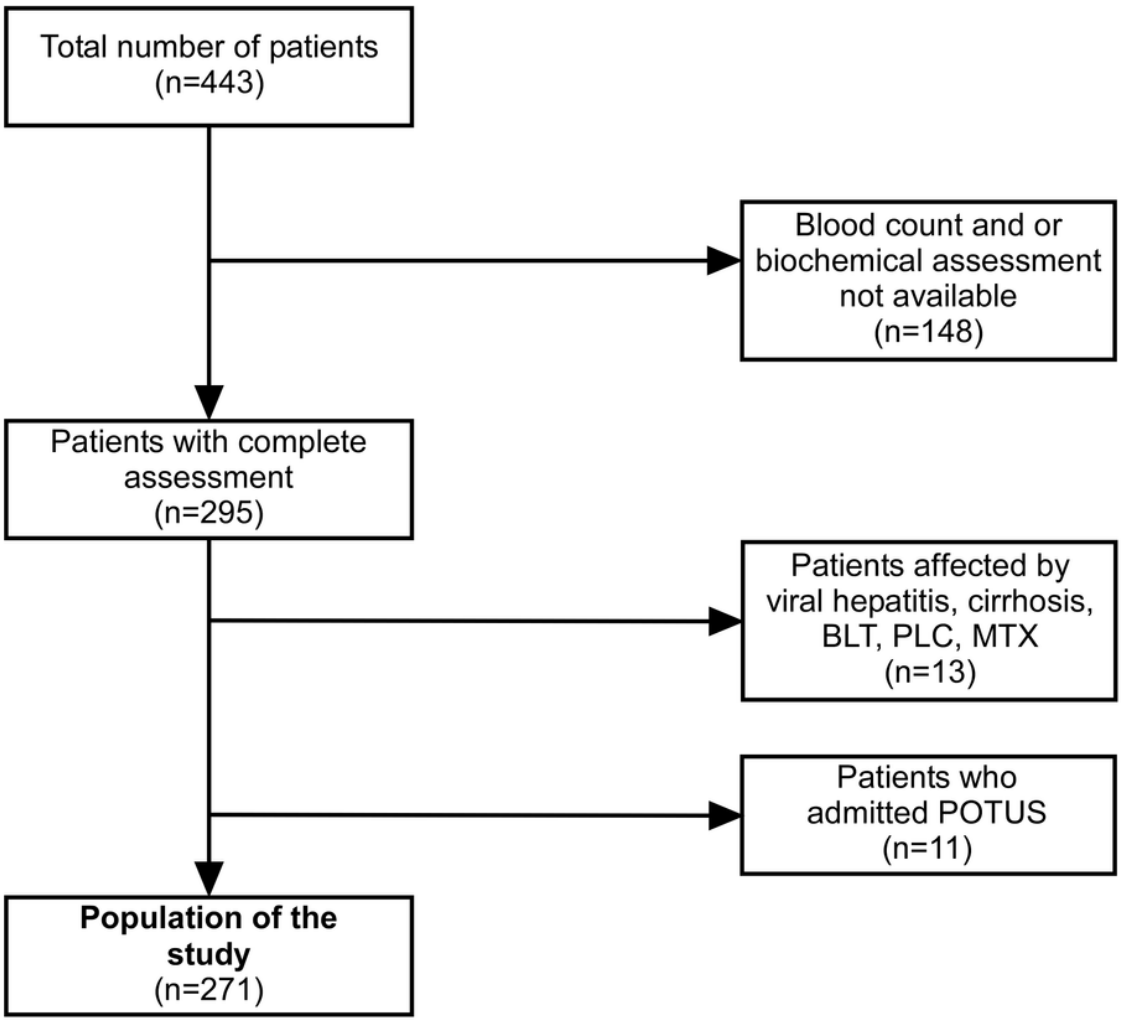

Figure 1

Figure 1

Flowchart of the study population.

Abbreviations: Benign Liver Tumours, BLT; Primary Liver Cancer, PLC; Hepatic Metastasis, MTX.

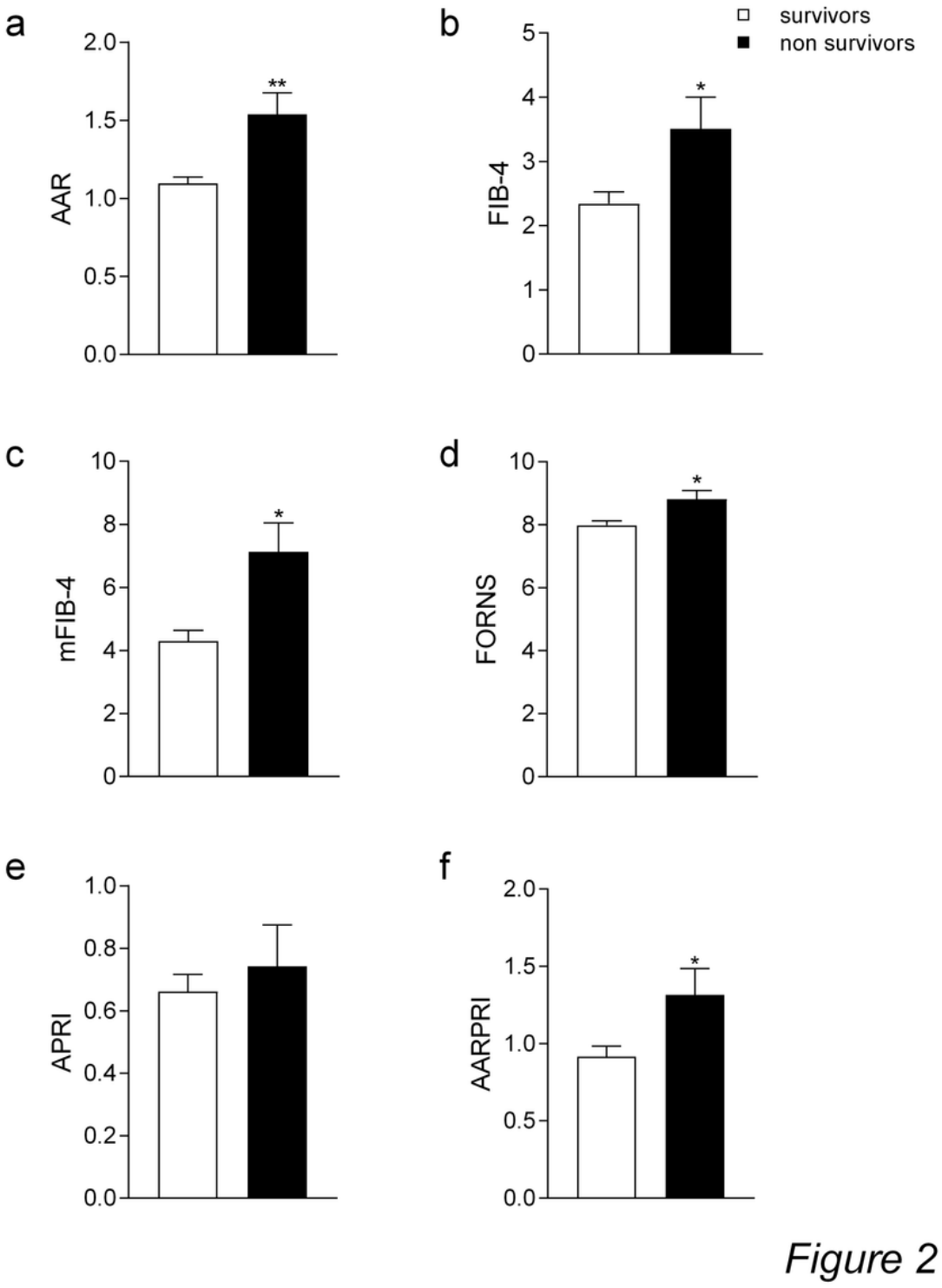

Figure 2

Comparison of Liver Fibrosis Scores in survivors and non survivors patients.

Data is presented as mean ± SEM. Statistical significance was assessed by Student T-test (*p<0.05, **p<0.001). Abbreviations: AST to ALT ratio, AAR; fibrosis 4 index, FIB-4; modified FIB-4, mFIB-4; AST to Platelet Ratio Index, APRI; AAR to Platelet ratio, AARPRI.

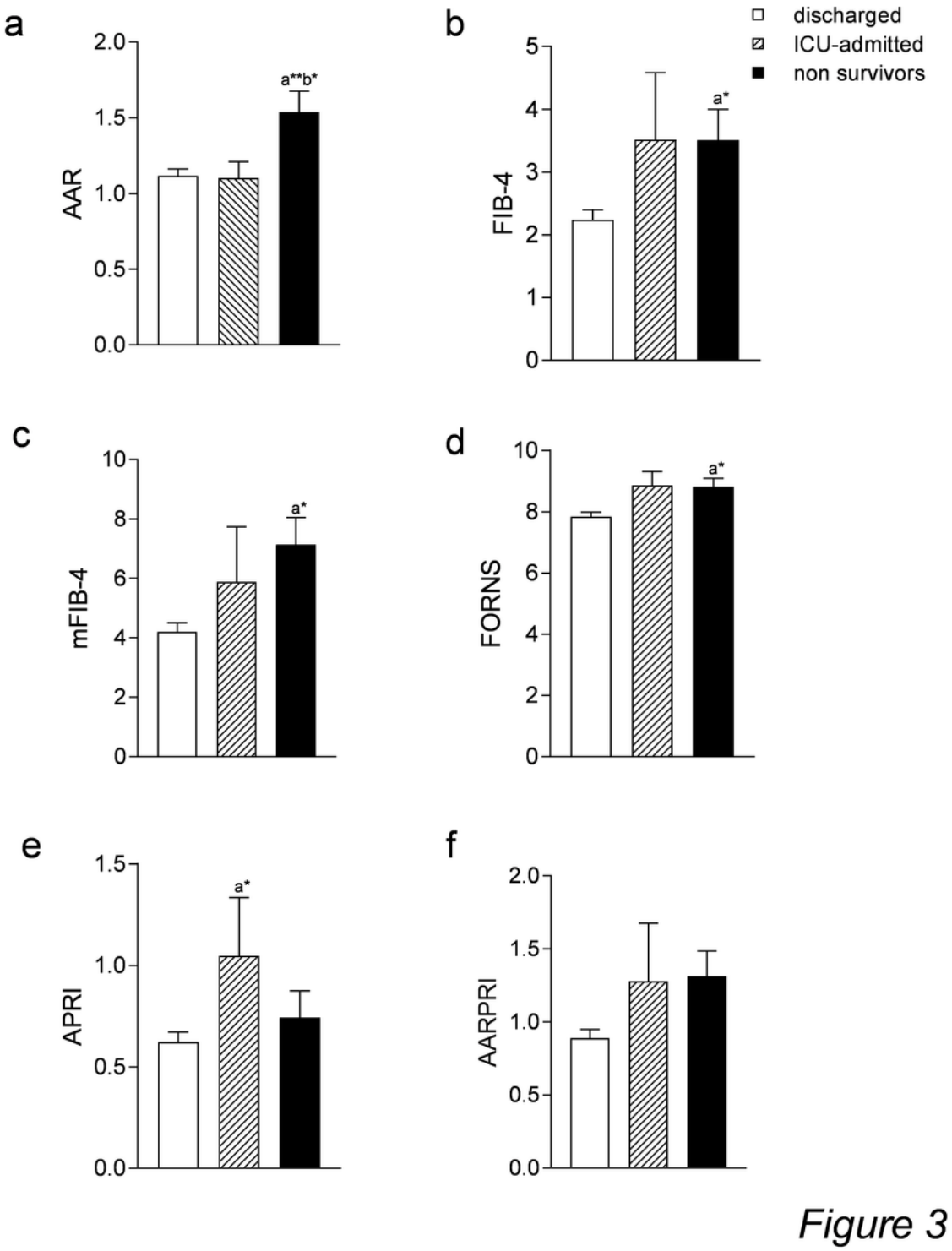

Figure 3

Figure 3

Comparison of Liver Fibrosis Scores among discharged, admitted to Intensive Care Unit (ICU), and non-survivor patients.

Data is presented as mean ± SEM. Comparisons were performed using one-way ANOVA test followed by Bonferroni's post-hoc test. Multiple comparison was performed by Student T-test. Lowercase letter

indicates significant difference (*p<0.05, **p<0.001) between two groups: (a) for discharged patients, (b) for ICU admitted patients. Abbreviations: AST to ALT ratio, AAR; fibrosis 4 index, FIB-4; modified FIB-4, mFIB-4; AST to Platelet Ratio Index, APRI; AAR to Platelet ratio, AARPRI.

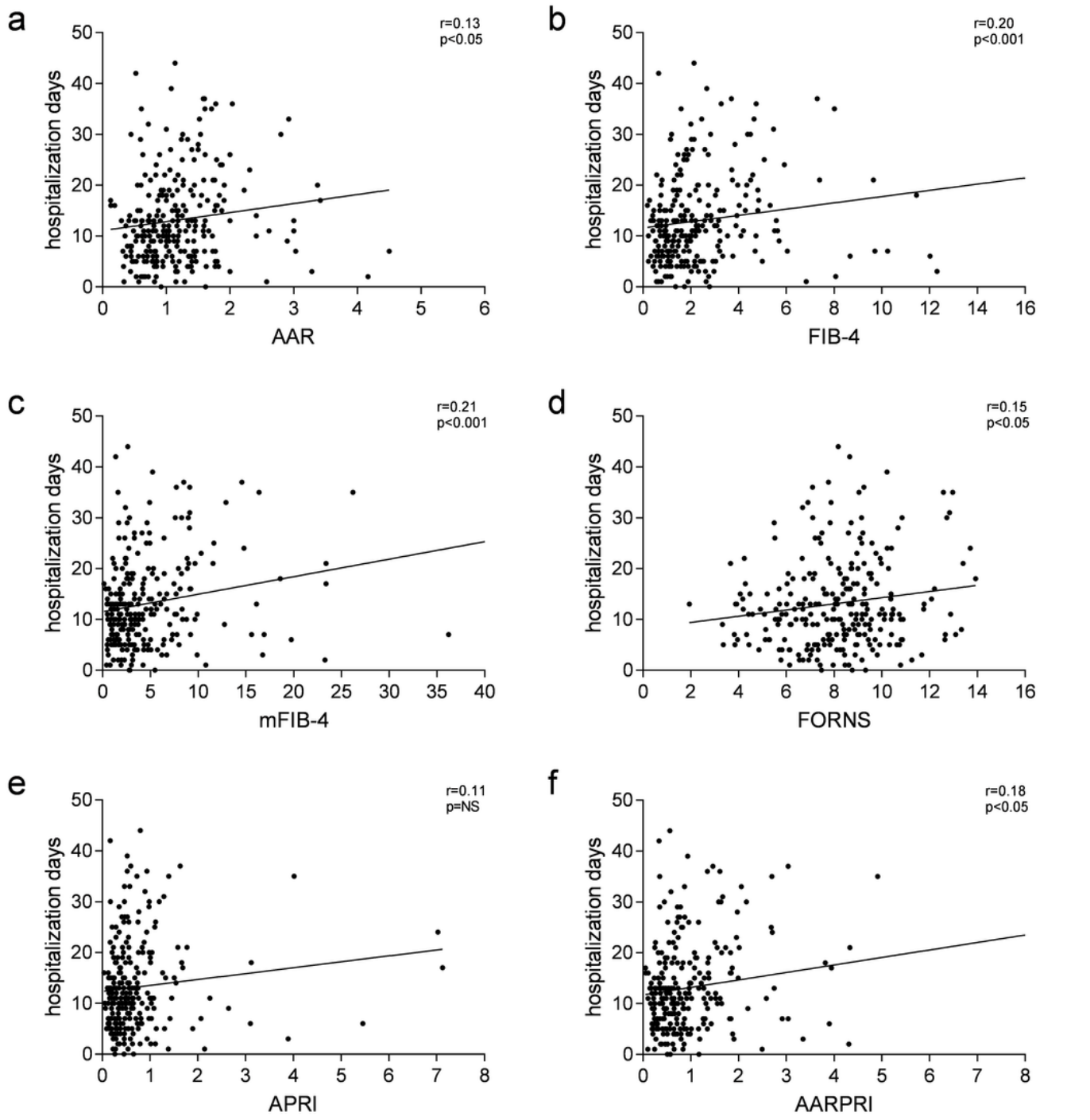

Figure 4

Figure 4

Correlation analysis of Liver Fibrosis Scores and hospitalization days in the whole population.

The correlation was analysed and estimated using Pearson's Correlation Coefficient (r). (p) indicates statistical significance. Abbreviations: AST to ALT ratio, AAR; fibrosis 4 index, FIB-4; modified FIB-4, mFIB-4; AAR to Platelet ratio, AARPRI.

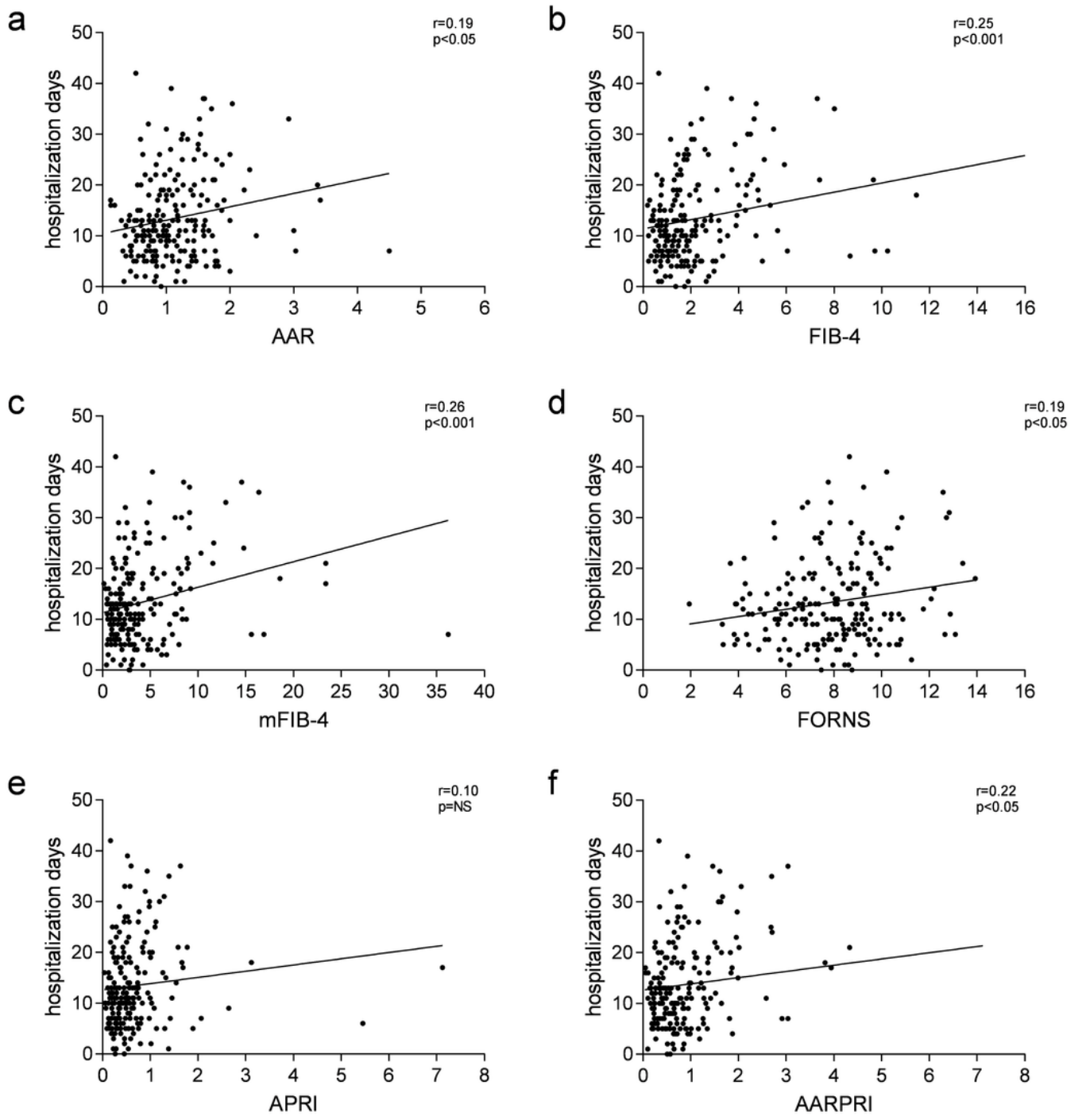

Figure 5

Figure 5

Correlation analysis of Liver Fibrosis Scores and hospitalization days in discharged patients.

The correlation was analysed and estimated using Pearson's Correlation Coefficient (r). (p) indicates statistical significance. Abbreviations: AST to ALT ratio, AAR; fibrosis 4 index, FIB-4; modified FIB-4, mFIB-4; AAR to Platelet ratio, AARPRI.

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