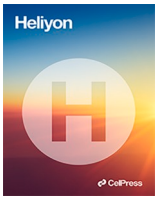
Heliyon 10 (2024) e25649

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

The FIB-4 scores in the emergency department to predict the outcomes of COVID-19 patients in taiwan

Chia-Yu Liu [c,1], San-Fang Chou [b,1], Pei-Ying Chiang [d,1], Jen-Tang Sun [e], Kuang-Chau Tsai [e], Fu-Shan Jaw [a], Chung-Ta Chang [e,f], Chieh-Min Fan [e], Yuan-Hui Wu [e], Peng-Yu Lee [e], Chia-Ying Hsieh [g], Jie-Ming Chen [e], Chien-Chieh Hsieh [a,e,f,h,i,*]

[a] Department of Biomedical Engineering, National Taiwan University, Taipei City, Taiwan
[b] Department of Medical Research, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[c] Department of Radiology, Taipei Veterans General Hospital, Taipei City, Taiwan
[d] Division of Hospital Medicine, Department of Internal Medicine, Far Eastern Memorial Hospital, Taiwan
[e] Department of Emergency Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[f] Graduate Institute of Medicine, Yuan Ze University, Taoyuan, Taiwan
[g] Department of Medical Education, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan
[h] Department of Emergency Medicine, Ten Chan General Hospital, Zhongli Dist, Taoyuan City, Taiwan
[i] International Bachelor Program in Electrical and Communication Engineering, Yuan Ze University, Taoyuan, Taiwan

ARTICLE INFO

Keywords:
Critical care medicine
Respiratory distress
COVID-19

ABSTRACT

Objective: We aimed to determine the reliability of using the Fibrosis-4 (FIB-4) index in COVID-19 patients without underlying liver illness.
Method: We employed multivariate logistic regression to identify variables that exhibited statistically significant influence on the ultimate outcome. Multilayer perceptron analysis was employed to develop a prediction model for the FIB-4 index concerning ICU admission and intubation rates. However, the scarcity of cases rendered the assessment of the mortality rate unfeasible. We plotted ROC curves to analyze the predictive strength of the FIB-4 index across various age groups.
Result: In univariate logistic regression, only the FIB-4 index and respiratory rate demonstrated statistical significance on all poor outcomes. The FIB-4 index for mortality prediction had an ROC and AUC of 0.863 (95% CI: 0.781–0.9444). It demonstrates predictive power across age groups, particularly for age ≥65 (AUC: 0.812, 95% CI: 0.6571–0.9673) and age <65 (AUC: 0.878, 95% CI: 0.8012–0.9558). Its sensitivity for intubation and ICU admission prediction is suboptimal.
Conclusion: FIB-4 index had promising power in prediction of mortality rate in all age groups.

* Corresponding author. Department of Biomedical Engineering, National Taiwan University, No. 1, Sec. 4, Roosevelt Rd., Da'an Dist., Taipei City, 106, Taiwan.
E-mail addresses: chiayuliu620@gmail.com (C.-Y. Liu), sfchou@femh.org.tw (S.-F. Chou), cpypei@gmail.com (P.-Y. Chiang), tangtang05231980@hotmail.com (J.-T. Sun), hikali@mail.femh.org.tw (K.-C. Tsai), jaw@ntu.edu.tw (F.-S. Jaw), chungta2001@gmail.com (C.-T. Chang), r92843017@ntu.edu.tw (C.-M. Fan), b101102106@tmu.edu.tw (P.-Y. Lee), ccandyppool@gmail.com (C.-Y. Hsieh), erich0793@gmail.com (J.-M. Chen), d10528022@gmail.com (C.-C. Hsieh).
[1] These authors contributed equally to the study.

https://doi.org/10.1016/j.heliyon.2024.e25649
Received 29 June 2023; Received in revised form 25 January 2024; Accepted 31 January 2024
Available online 14 February 2024

1. Introduction

Liver cirrhosis or fibrosis is a condition in which the liver tissue becomes scarred and stiff, resulting in the loss of normal functioning liver parenchyma [1]. It is a progressive and potentially life-threatening condition that can lead to liver malignancy and failure. However, there is growing evidence that liver cirrhosis is associated with COVID-19 infection [2]. Research has shown that COVID-19 patients with liver cirrhosis are at higher risk of developing severe respiratory failure and require hospitalization [3]. Understanding the effect of liver cirrhosis on COVID-19 is essential.

The Fibrosis-4 (FIB-4) index is a widely used clinical tool for assessing the severity of liver fibrosis (scarring) in patients with liver disease [4]. Four widely available laboratory values were used: age, aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels, and platelet count that comprise the index. The final score can be used to estimate the presence and extent of liver fibrosis and determine a patient's risk of progression to cirrhosis [5].

However, it is not well understood whether the FIB-4 index can be utilized as a predictive tool in COVID-19 patients without underlying liver diseases. Several mechanisms have been proposed for liver injury following COVID-19 infection [2,6]. When decompensation occurs, liver dysfunction may occur and progress to multiple organ failure [7]. Thus, we hypothesized that the FIB-4 index may be used as a clinical predictive tool for the severity of COVID-19, even though patients may not have an underlying impairment of hepatic function.

Using this premise, our research aims to define the usability of the FIB-4 index for COVID-19 patients without underlying liver disease in the emergency department. We would like to define the predictive power for poor clinical outcomes for COVID-19 patients without liver illness.

2. Methods

2.1. Study design

This was an observational study using a retrospective cohort. The research population comprised patients with COVID-19 infection who came to the emergency department [BLINDED FOR REVIEW], from May 1, 2021, to July 31, 2021. Our hospital is a tertiary medical center in Taiwan, and the average number of patients visiting the emergency department from May to July 2021 is 6993 people per month. The total number of people infected with COVID-19 in Taiwan between May and July 2021 was 15637.

The need to obtain informed consent was waived due to the retrospective nature of the study.

This study was approved by the Institutional Review Board of the Far-Eastern Memorial Hospital (number:110233-E).

2.2. Patient selection

Patients who visited the emergency department of the Hospital and were diagnosed with COVID-19 were included in the study. An oropharyngeal swab or nasopharyngeal swab was used for confirmation. The ICD-10 records from our database and electronic medical records were used for validation. We applied the following exclusion criteria: patients who had a record of refusal to participate in clinical trials, were transferred from other medical facilities, had more than one infectious disease diagnosed upon admission, had pre-existing liver diseases such as hepatitis B or C infection or liver cirrhosis, or who had died in our emergency department.

2.3. Data extraction

Basic study participant characteristics were extracted from the emergency department database. The medical histories of the included patients were retrieved from the electronic medical records and ICD-10 codes from our hospital database. Laboratory data were also collected. The FIB-4 index was calculated using the following formula:

$$[\text{age (years)} \times \text{AST (IU/L)}]/[\text{platelet count (10\^9/L)} \times \sqrt{\text{ALT (U/L)}}].$$

Due to a lack of AST data, the final count for FIB-4 was reduced to 160.

2.4. Outcome measures

The predictive power of the FIB-4 index for ICU admission to intensive care unit, endotracheal intubation, and mortality was evaluated.

2.5. Statistical analysis

The following methods were applied in our study. To compare patient characteristics, the Student's t-test was utilized for continuous variables. Conversely, we analyzed differences in categorical variables using the chi-square test. If the calculated two-tailed p-value was less than 0.05, it was considered statistically significant. The Shapiro-Wilk test was used to confirm the normal distribution of continuous variables.

The minimum sample size was calculated by using the method proposed by Riley et al. [8]. The predictive power of the FIB-4 index

on COVID-19 infected poor outcomes was evaluated using receiver operating curve (ROC) analysis. The area under the curve, sensitivity, and specificity of each prediction model were analyzed. The optimal cutoff point for each model was determined by applying Youden's J statistic (calculated as sensitivity-(1-specificity) for each observer point) [9]. Statistical analysis was performed using the RStudio software with one tailed P-value (version 1.4.1717) [10]. We also used univariate logistic regression and multivariate logistic regression to check the significance of FIB-4 and other factors. Multilayer perceptron analysis was employed to develop a prediction model for the FIB-4 index concerning ICU admission and intubation rates.

3. Results

3.1. Characteristics of included patients

Table 1 summarizes the demographic information and laboratory values. This study included 221 patients (119 male and 102 female). The mean age of the patients was 61. Comorbidity and laboratory data were also shown.

For calculating the minimum sample size, the number of predictor parameters was 4, the expected R2 was set at 0.3, and the level of shrinkage at internal validation was assumed to be at least 0.9. The calculated minimum sample size required was 204.

Table 2 shows the normality of numerical data was tested by Kolmogorov-Smirnov test. The statistics result of non-normally-distributed data was expressed as median (Q1, Q3). Categorical data was expressed as frequency and percentage. Table 3 reveals the associations of patient characteristics with the categorical outcomes analyzed by univariate logistic regression. Statistically significant differences were observed in the triage lever, age, respiratory rate, diastolic blood pressure and SpO2, platelet count, Leukocyte counts, AST, ALT, CRP, D-dimer, C-reactive protein, potassium and sodium levels. The FIB-4 index is significant in the ICU admission group, intubation group and mortality group. All continuous variables were normally distributed after confirmation using the Shapiro-Wilk test.

3.2. The ROC for predicting poor outcomes using the FIB-4 index

Fig. 1 show the ROC curves of mortality rate with subgroup analysis on age less or more than 65 using the FIB-4 index. The area under the curve was 86.30 % (95% C.I. % 78.1%–94.44%) for mortality of all patients, 81.2 % (95% C.I. 65.7%–96.7%) for age over 65,

Table 1
The demographic and clinical characteristics of enrolled COVID-19 patients (N = 221).

Characteristic	Statistics	Sample size	Min-Max
Triage			
Level 1	29 (13.1%)	221	
Level 2	35 (15.8%)	221	
Level 3	126 (57.0%)	221	
Level 4	17 (7.7%)	221	
Level 5	14 (6.3%)	221	
Age (year), median	61 (46, 68)	221	25–89
Biological sex, male	119 (53.8%)	221	
Body weight (kg)	66.4 (57.9, 74.75)	221	37–115
Body temperature (°C)	36.7 (36.2, 37.2)	220	34.9–40.1
Heart rate (times/min)	101.03 ± 20.80	219	53–165
Respiratory Rate (times/min)	20 (18, 20)	220	16–50
Systolic blood pressure (mmHg)	128 (114, 149)	219	54–215
Diastolic blood pressure (mmHg)	78 (68, 92)	219	11–142
SpO2 in ER (%)	96 (94, 98)	219	36–100
Lab blood test data			
Leukocyte counts (10^3/μL)	6.18 (4.96, 8.16)	221	1.93–19.65
Platelet (10^3/μL)	191 (145, 250)	221	56–728
AST (U/L)	30 (21, 40)	160	9–406
ALT (U/L)	21 (14, 36.5)	221	3–257
D-Dimer (ng/mL FEU)	520 (327.5, 941)	221	4.7 to >10,000
CRP (mg/dL)	3.27 (0.64, 7.79)	221	0.0029–30.87
Creatinine (mg/dL)	0.84 (0.69, 1.06)	221	0.36–71.00
Sodium (mmol/L)	135 (132, 138)	221	115–144
Potassium (mmol/L)	3.7 (3.4, 4.0)	221	2.6–7.0
FIB-4 score	1.91 (1.12, 3.07)	160	0.27–22.82
Comorbidity			
Malignancy/Hematological disorder	5 (3.5%)	143	
Cardiovascular disorder	76 (53.1%)	143	
Hypertension	72 (50.3%)	143	
Diabetes mellitus	31 (21.7%)	143	
Renal insufficiency	4 (2.8%)	143	

The normality of numerical data was tested by Kolmogorov-Smirnov test. Normally-distributed data are expressed as mean ± standard deviation while non-normally-distributed data was expressed as median (Q1, Q3). Categorical data was expressed as frequency and percentage.

Table 2
The outcomes of patients in intubation, ICU admission, ICU-days, general ward days, hospital days and mortality. N = 221.

Outcomes	Statistics	Sample size	Min-Max
Intubation	27 (12.2%)	221	
ICU admission	47 (21.3%)	221	25–89
ICU days	13 (6.25, 18.75)	48	3–68
General ward days	11 (8, 15)	218	2–45
Hospital days	12 (10, 17)	221	8–82
Mortality	10 (4.5%)	221	

The normality of numerical data was tested by Kolmogorov-Smirnov test. The statistics result of non-normally-distributed data was expressed as median (Q1, Q3). Categorical data was expressed as frequency and percentage.

Table 3
The associations of patient characteristics with the categorical outcomes were analyzed by univariate logistic regression.

Variables	Intubation	ICU admission	Mortality
	Odds ratio, p value	Odds ratio, p value	Odds ratio, p value
Triage levels	3.893, $p < 0.001$*	3.884, $p < 0.001$*	1.899, $p = 0.058$
Age (year), median	1.052, $p = 0.005$*	1.040, $p = 0.004$*	1.066, $p = 0.005$*
Biological sex, male	2.232, $p = 0.071$	1.685, $p = 0.124$	2.062, $p = 0.304$
Body weight (kg)	1.032, $p = 0.094$	1.017, $p = 0.137$	1.021, $p = 0.311$
Body temperature (°C)	1.022, $p = 0.928$	1.066, $p = 0.735$	1.247, $p = 0.524$
Heart rate (times/min)	0.999, $p = 0.947$	1.015, $p = 0.066$	0.996, $p = 0.776$
Respiratory Rate (times/min)	1.303, $p = 0.004$*	1.326, $p = 0.001$*	1.157, $p = 0.036$*
Systolic blood pressure (mmHg)	0.987, $p = 0.111$	0.997, $p = 0.603$	0.981, $p = 0.148$
Diastolic blood pressure (mmHg)	0.963, $p = 0.002$*	0.983, $p = 0.052$	0.963, $p = 0.025$*
SpO2 in ER (%)	0.864, $p < 0.001$*	0.836, $p < 0.001$*	0.959, $p = 0.120$
Lab data			
Leukocyte counts (10^3/μL)	1.136, $p = 0.031$*	1.110, $p = 0.040$*	0.851, $p = 0.258$
Platelet (10^3/μL)	0.994, $p = 0.051$	0.994, $p = 0.017$*	0.976, $p = 0.002$*
AST (U/L)	1.009, $p = 0.058$	1.036, $p < 0.001$*	1.009, $p = 0.052$
ALT (U/L)	1.014, $p = 0.017$*	1.027, $p < 0.001$*	1.012, $p = 0.077$
D-Dimer[a] (ng/mL FEU)	2.481, $p < 0.001$*	2.592, $p < 0.001$*	1.068, $p = 0.835$
CRP (mg/dL)	1.153, $p < 0.001$*	1.153, $p < 0.001$*	1.072, $p = 0.106$
Creatinine (mg/dL)	1.008, $p = 0.827$	0.995, $p = 0.889$	1.023, $p = 0.548$
Sodium (mmol/L)	0.909, $p = 0.016$*	0.928, $p = 0.030$*	0.925, $p = 0.188$
Potassium (mmol/L)	3.423, $p = 0.001$*	1.809, $p = 0.047$*	2.830, $p = 0.018$*
FIB-4 score	1.251, $p = 0.005$*	1.224, $p = 0.008$*	1.382, $p = 0.002$*
Comorbidity			
Malignancy/Hematological disorder	2.214, $p = 0.491$	2.506, $p = 0.327$	0.000, $p = 0.999$
Cardiovascular disorder	6.706, $p = 0.015$*	1.289, $p = 0.536$	1.385E+8, $p = 0.997$
Hypertension	7.602, $p = 0.009$*	1.763, $p = 0.171$	5.224, $p = 0.136$
Diabetes mellitus	7.227, $p < 0.001$*	3.772, $p = 0.003$*	8.148, $p = 0.019$*
Renal insufficiency	2.976, $p = 0.359$	3.793, $p = 0.192$	8.933, $p = 0.078$

[a] the level of D-dimer over 10,000 was set as 11,000 for statistical calculation, and all of the data of D-dimer were transformed by natural log.

and 87.8% (95% C.I. 80.1%–95.5%) for ages under 65, respectively. Additionally, the optimal cutoff values were 2.77 for all patients, 4.1 for age over 65. The details are summarized in Table 4 (see Figs. 2 and 3)

Figs. 4 and 5 reveal the ROC curves and AUC areas for intubation and ICU admission prediction were examined with the affective factors ALT, CRP and D-Dimer by neural networks\multilayer Perceptron analysis. The area under the curve was 85.40 % for prediction of intubation, and 84.2 % for prediction of ICU admission.

4. Discussion

Our study investigated the association between the liver fibrosis index and the poor prognosis of COVID-19. We found that the liver fibrosis index, as measured using the FIB-4 index, was significantly associated with the risk of poor prognosis, including ICU admission, mechanical ventilation, and mortality, in COVID-19 patients without underlying liver diseases. Our results are consistent with those of previous studies that demonstrated the predictive value of liver function tests, such as ALT and AST levels, for COVID-19 infection [11–14]. The liver is a target organ of the SARS-CoV-2 virus and is often affected by the inflammatory response to the infection. Liver injury has also been reported in COVID-19 patients. As expected, this correlation was associated with poorer outcomes. However, the mechanism underlying elevated AST and ALT levels in such patients remains unclear [15].

For SARS-CoV-2 virus, angiotensin converting enzyme 2, which is also expressed in the liver, is a key receptor for viral invasion. The virus may directly damage the liver via this mechanism. In addition, cytokine storms caused by severe immune responses may play a role in disease progression. The mixed effects of endotheliopathy/coagulopathy, platelet dysfunction, and multiple inflammatory

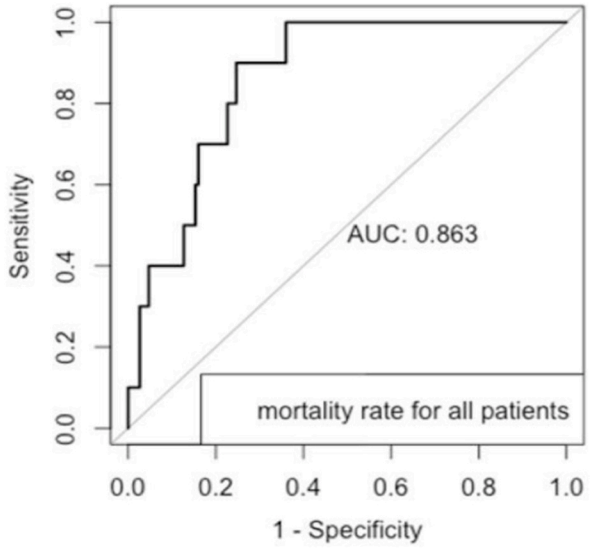


Fig. 1. ROC summary for FIB-4 scores for predicting mortality of all patients.

Table 4
ROC of predictive power of FIB-4 index on mortality rate with subgroup analysis on age less or more than 65.

	Area under curve	Optimal cutoff	sensitivity	Specificity
All patient	0.863 (95% CI: 0.781–0.9444) $p < 0.001$	2.77	0.900	0.753
Age $\geq$ 65	0.812 (95% CI: 0.6571–0.9673) $p < 0.001$	4.10	0.857	0.685
Age <65	0.878 (95% CI: 0.8012–0.9558) $P < 0.001$	2.74	1.00	0.844

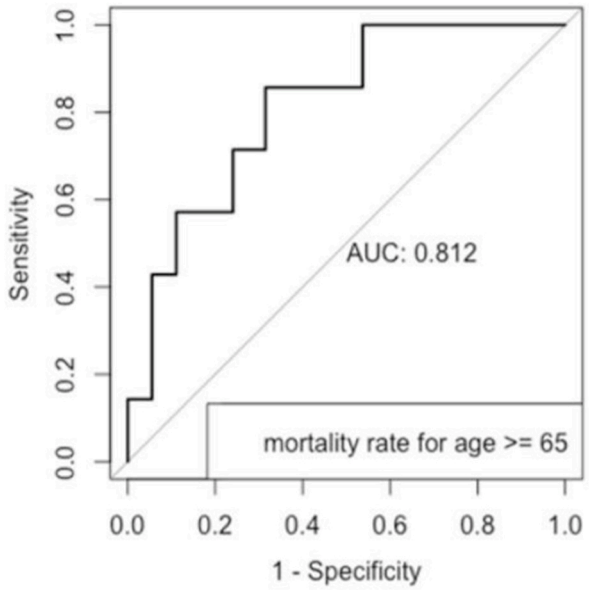


Fig. 2. ROC summary for FIB-4 scores for predicting mortality of patients>65 years old.

responses can lead to irreversible damage in viral hosts [15]. However, severe hepatic injury and liver failure are uncommon. Most COVID-19 patients with elevated liver enzyme levels experience only mild liver dysfunction. However, the long-term post-infection effects remain unknown [16]. This finding suggests that the correlation between liver injury and COVID-19 is multifactorial.

Previous studies have suggested a correlation between liver fibrosis severity and COVID-19 [17]. Our study demonstrates that the

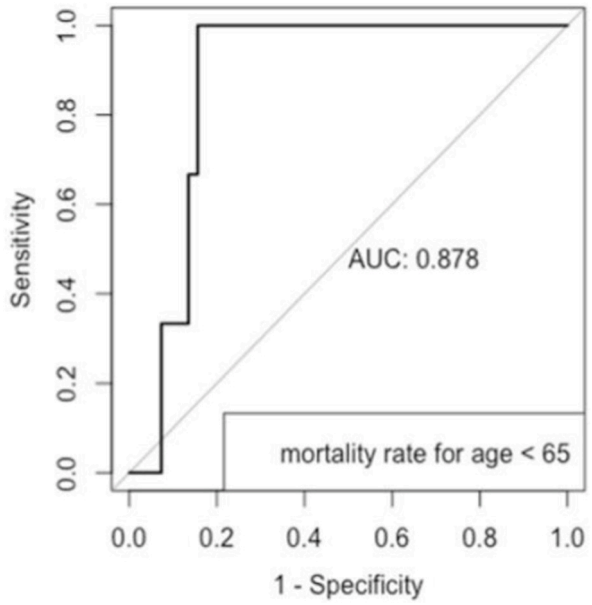


Fig. 3. ROC summary for FIB-4 scores for predicting mortality of patients<65 years old Sen, sensitivity; Spe, specificity, ROC, receiver operating characteristic curve.

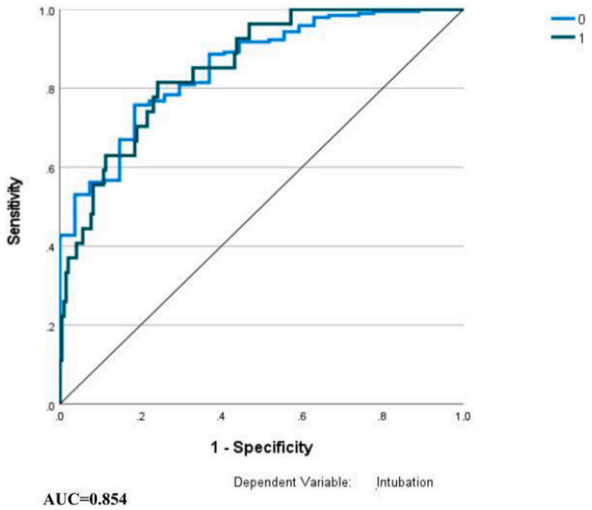


Fig. 4. FIB-4 score for intubation ROC curves and AUC areas for prediction of intubation were examined with the affective factors ALT, CRP and D-Dimer by neural networks\multilayer Perceptron analysis.

FIB-4 index may serve as a genuine predictor of infection severity, even in patients without chronic liver disease. The results provide robust evidence for the utilization of the FIB-4 index in the general population or specific communities. The FIB-4 index is a non-invasive and widely available tool that can be easily calculated from routine blood tests, making it feasible for clinical use in the context of COVID-19 infection, even in the emergency department.

In addition, to the best of our knowledge, our study is the first to establish a prediction model using the FIB-4 index in the emergency department for general poor outcomes after COVID-19 infection in an Asian population without underlying liver impairment. Previous studies have also supported the correlation between the FIB-4 index and COVID-19 mortality [18–20]. A study by Rome et al. utilized the FIB-4 index to sketch ROC and provided promising results [21]. We confirmed this correlation and provided a reference value for clinicians to rapidly triage incoming patients from different populations. By performing simple laboratory examinations, unfavorable clinical outcomes can be anticipated, even in patients without underlying liver diseases. We can provide rapid triage and intervention for these patients, which is important in crowded emergency room settings, to prevent deterioration.

Based on the tradeoff between sensitivity and specificity using the Youden index. These cutoff points had sensitivities >70% for

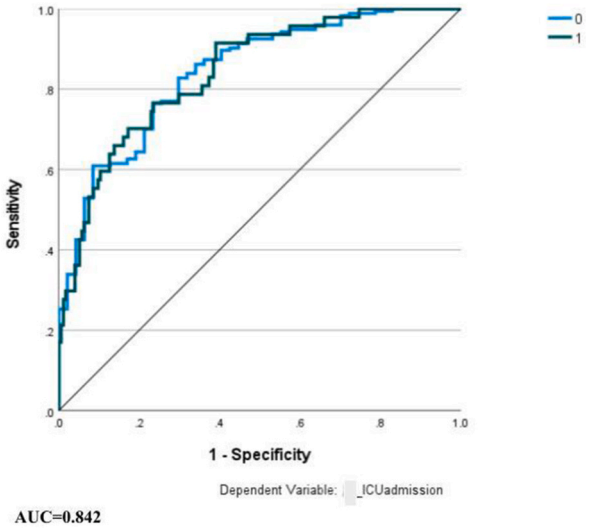


Fig. 5. FIB-4 score for intensive care unit ROC curves and AUC areas for prediction of ICU admission were examined with the affective factors ALT, CRP and D-Dimer by neural networks\multilayer Perceptron analysis.

predicting poor prognosis. This suggests that the liver fibrosis index may be useful as a complementary tool to other clinical and laboratory parameters for identifying patients at high risk of poor prognosis but should not be used as a sole diagnostic test. A more precise management algorithm was developed by integrating the results of the FIB-4 index.

Nevertheless, our study had some limitations that should be acknowledged. First, the sample size was not sufficiently large, and the generalizability of our findings to other populations and settings must be confirmed. Second, we did not have complete information on the baseline liver function and underlying liver diseases of the patients, which may have confounded the association between the liver fibrosis index and poor prognosis. Third, we did not compare the performance of the liver fibrosis index with other prognostic models or scores, such as the SOFA or APACHE II scores, which are widely used in the ICU setting. Fourth, if the patient is currently taking hepatotoxic medications such as oral nirmatrelvir/ritonavir (Paxlovid®), the effect should be considered. However, the FIB-4 score was checked before administering antiviral drugs in the emergency department. It is unlikely that all subjects with a drug history of such properties were excluded. The use of acetaminophen, isoniazid, and amiodarone may have caused a bias in the results. However, we believe that excluding patients taking hepatotoxic medications limits the generalizability of this study. These populations were included in our analysis. Finally, the retrospective nature of our study may have resulted in inevitable bias. For example, selection bias of the included subjects may lead to inaccurate conclusions and should be carefully considered and addressed.

In conclusion, our study suggests that the liver fibrosis index, as measured using the FIB-4 index, can predict poor prognosis in COVID-19 patients without underlying liver diseases, even in the emergency department. The FIB-4 index had promising power in prediction of mortality rate on all age groups. These non-invasive and easily calculated indices may be useful as complementary tools to other clinical and laboratory parameters to identify high-risk patients and guide clinical decision-making. We have also discovered that the HASI index [22], or Age Shock Index [23], can predict the outcomes of COVID-19 patients in emergency department. Further studies are necessary to validate our findings and explore the potential mechanisms underlying the association between liver fibrosis and covid-19 patients.

Funding

This study was supported by a grant from Far Eastern Memorial Hospital (FEMH-2023-C-043).

The English editing of this article was sponsored by National Taiwan University with the support of Higher Education Sprout Project from the Ministry of Education, Taiwan.

Ethical approval

This study was approved by the Institutional Review Board of the Far-Eastern Memorial Hospital (number: 110233-E).

CRediT authorship contribution statement

Chia-Yu Liu: Writing – original draft, Formal analysis. **San-Fang Chou:** Writing – review & editing, Data curation. **Pei-Ying Chiang:** Writing – original draft, Data curation. **Jen-Tang Sun:** Supervision, Methodology. **Kuang-Chau Tsai:** Conceptualization. **Fu-Shan Jaw:** Resources, Methodology. **Chung-Ta Chang:** Methodology. **Chieh-Min Fan:** Conceptualization. **Yuan-Hui Wu:** Investigation, Supervision. **Peng-Yu Lee:** Data curation. **Chia-Ying Hsieh:** Software. **Jie-Ming Chen:** Writing – review & editing, Data

curation. **Chien-Chieh Hsieh:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Chien Chieh Hsieh reports article publishing charges was provided by Far Eastern Memorial Hospital. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We pay tribute to all dedicated frontline health care professionals during the COVID-19 pandemic.
The authors wish to thank Ms. Szu-Ting Liu and Ms. Yin-Chen Yeh for extracting data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25649.

References

[1] P. Ginès, A. Krag, J.G. Abraldes, E. Solà, N. Fabrellas, P.S. Kamath, Liver cirrhosis, Lancet 398 (10308) (2021) 1359–1376, https://doi.org/10.1016/S0140-6736(21)01374-X.
[2] D. Yu, Q. Du, S. Yan, X.-G. Guo, Y. He, G. Zhu, et al., Liver injury in COVID-19: clinical features and treatment management, Virol. J. 18 (1) (2021) 121, https://doi.org/10.1186/s12985-021-01593-1.
[3] M. Liu, K. Mei, Z. Tan, S. Huang, F. Liu, C. Deng, et al., Liver fibrosis scores and hospitalization, mechanical ventilation, severity, and Death in patients with COVID-19: a systematic review and dose-response meta-analysis, Chin. J. Gastroenterol. Hepatol. 2022 (2022) 7235860, https://doi.org/10.1155/2022/7235860.
[4] A. Blanco-Grau, P. Gabriel-Medina, F. Rodriguez-Algarra, Y. Villena, R. Lopez-Martínez, S. Augustín, et al., Assessing liver fibrosis using the FIB4 index in the community setting, Diagnostics 11 (2021) 2236, https://doi.org/10.3390/diagnostics11122236.
[5] Y. Sumida, M. Yoneda, H. Hyogo, Y. Itoh, M. Ono, H. Fujii, et al., Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population, BMC Gastroenterol. 12 (2012) 2, https://doi.org/10.1186/1471-230X-12-2.
[6] G.R. Sivandzadeh, H. Askari, A.R. Safarpour, F. Ejtehadi, E. Raeis-Abdollahi, A. Vaez Lari, et al., COVID-19 infection and liver injury: clinical features, biomarkers, potential mechanisms, treatment, and management challenges, World J Clin Cases 9 (2021) 6178–6200, https://doi.org/10.12998/wjcc.v9.i22.6178.
[7] S. Zaim, J.H. Chong, V. Sankaranarayanan, A. Harky, COVID-19 and multiorgan response, Curr. Probl. Cardiol. 45 (2020) 100618, https://doi.org/10.1016/j.cpcardiol.2020.100618.
[8] R.D. Riley, K.I. Snell, J. Ensor, D.L. Burke, F.E. Harrell Jr., K.G. Moons, et al., Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes, Stat. Med. 38 (7) (2019) 1276–1296, https://doi.org/10.1002/sim.7992.
[9] R. Fluss, D. Faraggi, B. Reiser, Estimation of the Youden Index and its associated cutoff point, Biom. J. 47 (4) (2005) 458–472, https://doi.org/10.1002/bimj.200410135.
[10] R. Team, RStudio: Integrated Development Environment for R, Public Benefit Corporation, 2021.
[11] D. Crisan, L. Avram, C. Grapa, A. Dragan, D. Radulescu, S. Crisan, et al., Liver injury and elevated FIB-4 define a high-risk group in patients with COVID-19, J. Clin. Med. 11 (2021) 153, https://doi.org/10.3390/jcm11010153.
[12] R. Lombardi, V. Mura, A. Cespiati, F. Iuculano, G. Sigon, G. Pallini, et al., Usefulness of fibrosis-4 (FIB-4) score and metabolic alterations in the prediction of SARS-CoV-2 severity, Intern Emerg Med 17 (2022) 1739–1749, https://doi.org/10.1007/s11739-022-03000-1.
[13] P. Ruggeri, A. Esquinas, Fibrosis-4 (FIB-4) index and mortality in COVID-19 patients admitted to the emergency department: a new interesting predictive index for patients with COVID-19 disease? Inter emerg med 17 (2022) 2451–2452, https://doi.org/10.1007/s11739-022-03067.
[14] M.L. Grigoras, I.M. Citu, C. Citu, V.D. Chiriac, F. Gorun, M.C. Levai, et al., Evaluation of FIB-4, NFS, apri and liver function tests as predictors for SARS-CoV-2 infection in the elderly population: a matched case-control analysis, J. Clin. Med. 11 (2022) 5149, https://doi.org/10.3390/jcm11175149.
[15] M.J. McConnell, R. Kondo, N. Kawaguchi, Y. Iwakiri, Covid-19 and liver injury: role of inflammatory endotheliopathy, platelet dysfunction, and thrombosis, Hepatol Commun 6 (2022) 255–269, https://doi.org/10.1002/hep4.1843.
[16] H.E. Davis, L. McCorkell, J.M. Vogel, E.J. Topol, Long COVID: major findings, mechanisms and recommendations, Nat. Rev. Microbiol. 21 (3) (2023) 133–146, https://doi.org/10.1038/s41579-022-00846.
[17] R. Nagarajan, Y. Krishnamoorthy, S. Rajaa, V.S. Hariharan, COVID-19 severity and mortality among chronic liver disease patients: a systematic review and meta-analysis, Prev. Chronic Dis. 19 (2022) E53, https://doi.org/10.5888/pcd19.210228.
[18] L. Ibáñez-Samaniego, F. Bighelli, C. Usón, C. Caravaca, C. Fernández Carrillo, M. Romero, et al., Elevation of liver fibrosis index FIB-4 is associated with poor clinical outcomes in patients with COVID-19, J. Infect. Dis. 222 (2020) 726–733, https://doi.org/10.1093/infdis/jiaa355.
[19] R.K. Sterling, T. Oakes, T.S. Gal, M.P. Stevens, M. deWit, A.J. Sanyal, The fibrosis-4 index is associated with need for mechanical ventilation and 30-day mortality in patients admitted with coronavirus disease 2019, J. Infect. Dis. 222 (2020) 1794–1797, https://doi.org/10.1093/infdis/jiaa550.
[20] Y. Li, J. Regan, J. Fajnzylber, K. Coxen, H. Corry, C. Wong, et al., Liver fibrosis index FIB-4 is associated with mortality in COVID-19, Hepatol Commun 5 (2021) 434–445, https://doi.org/10.1002/hep4.1650.
[21] T. Bucci, G. Galardo, O. Gandini, T. Vicario, C. Paganelli, S. Cerretti, et al., Fibrosis-4 (FIB-4) Index and mortality in COVID-19 patients admitted to the emergency department, Intern Emerg Med 17 (2022) 1777–1784, https://doi.org/10.1007/s11739-022-02997-9.
[22] C.C. Hsieh, C.Y. Liu, K.C. Tsai, F.S. Jaw, J. Chen, The hypoxia-age-shock index at triage to predict the outcomes of Covid-19 patients, Am J Emerg Med 65 (2023 Mar) 65–70, https://doi.org/10.1016/j.ajem.2022.12.034.
[23] C.C. Hsieh, M.J. Ting, C.T. Chang, K.C. Tsai, Y.Y. Huang, F.S. Jaw, et al., Is the Shock Index Associated with Adverse Outcomes among Geriatric Patients with COVID-19 in the Emergency Department Triage? Int. J. Gerontol. 17 (3) (2023) 177–182, https://doi.org/10.6890/IJGE.202307_17(3).0007.