RESEARCH ARTICLE

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Optimizing Prognostic Precision in Hepatocellular Carcinoma: Integrating PWR with ALBI and PALPI Scores

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Abstract

Background: Enhancing prognostication in Hepatocellular Carcinoma (HCC) remains an unmet need, especially in patients with preserved liver function. This study aimed to integrate the Platelet-to-White Blood Cell Ratio (PWR) with albumin-bilirubin (ALBI) and platelets-albumin-bilirubin (PALBI) scores for improved assessment of mortality and treatment responses in hepatocellular carcinoma (HCC) patients. **Methods:** In this prospective study, 262 patients with hepatocellular carcinoma (HCC) were included, with basic data collected and followed up for one year or until death. All prognostic scores were calculated by integrating the PWR with the ALBI and PALBI scores, examining their relationship with treatment responses and mortality rates. **Results:** The patients were mainly males (69.5%), aged 59.6 ± 8.09 years. The predictive power of the integrated PALBI+PWR score at different time points 1 (P 0.004), 3 months, and 6 months (P 0.004) overpowered all other scores. However, late at the 12-month follow-up, ALBI score had reported superiority on PALPI+PWR (AUC 0.631, 0.617), respectively. Regression analyses confirmed the high performance of PALBI+PWR factors in influencing treatment response (P 0.009–OR 0.562 (0.365 – 0.867)). Regarding mortality prediction, PALPI+PWR proved the highest efficacy in regression analysis (P <0.001) OR (2.451 (1.555 – 3.862). **Conclusion:** Integrating PWR with the PALBI score enhances prognostic precision in patients with HCC, offering improved predictive power for treatment responses and mortality in the early stages of HCC with preserved liver function.

Keywords: Platelets White Blood Cell Ratio- ALBI score- PALBI score- Hepatocellular Carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is a prevalent and aggressive form of liver cancer, representing a significant global health burden due to its high morbidity and mortality rates [1]. Effective management of HCC hinges on accurate prognostication and evaluation of treatment responses, which are essential for tailoring therapeutic strategies and improving patient outcomes. Despite advances in diagnostic and therapeutic modalities, the heterogeneous nature of HCC complicates prognostic assessment.

The albumin-bilirubin (ALBI) score, introduced to refine liver function assessment, has been extensively studied and validated as a predictive tool in HCC [2]. The ALBI score leverages serum albumin and bilirubin levels to objectively measure liver function and has shown utility in predicting survival and treatment outcomes in HCC patients. However, its accuracy is often questioned in early-stage HCC cases, where albumin and bilirubin levels may remain within normal ranges, thus diminishing its prognostic precision. This limitation underscores the need for more robust and comprehensive prognostic models.

In response to these limitations, the platelets-albumin-bilirubin (PALBI) score was developed by integrating platelet counts into the ALBI score [3]. The inclusion of platelet counts enhances the prognostic value of the score, as thrombocytopenia is a common hematologic abnormality in HCC patients, often associated with advanced liver disease and portal hypertension. The PALBI score has demonstrated superior prognostic performance compared to the ALBI score alone, highlighting the significance of haematological parameters in the prognostic assessment of HCC.

Recent research has further illuminated the role of haematological indices in the progression and prognosis of HCC. There is accumulating evidence indicating that haematological abnormalities, such as thrombocytopenia and leukopenia, are early indicators of HCC complicating liver cirrhosis [4]. Thrombocytopenia emerges as the most prevalent and initial hematologic abnormality, often followed by leukopenia. These findings suggest that haematological indices not only reflect the severity of liver disease but also have independent prognostic value.

In this context, the platelet-to-white blood cell ratio (PWR) has emerged as a promising marker for predicting

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morbidity and mortality in liver disease, including hepatitis B virus infection and acute-on-chronic liver failure [5-7]. The PWR combines platelet counts and white blood cell counts, providing a composite measure that reflects both thrombocytopenia and leukopenia. Given its proven prognostic value in other liver conditions, the potential utility of PWR in HCC warrants further investigation [8].

Despite these advances, there remains a gap in the comprehensive evaluation of combined hematologic and biochemical markers for prognostication in HCC. Integrating PWR with the ALBI and PALBI scores could provide a more nuanced and accurate assessment of prognosis, addressing the limitations of existing scores and offering better predictive power for mortality and treatment responses. The rationale behind this integration lies in the biological plausibility that combining hematologic and biochemical markers can capture the multifaceted nature of HCC progression and patient outcomes more effectively.

This study aims to bridge this gap by investigating the prognostic value of PWR in HCC and examining the current evidence on the integration of PWR with ALBI and PALBI scores. By highlighting the potential benefits of this combined approach, we seek to enhance the precision of prognostic models in predicting mortality and treatment responses in HCC patients. This integrated approach could represent a significant step forward in the management of HCC, offering clinicians a more reliable tool for patient stratification and therapeutic decision-making.

Materials and Methods

Patients and Procedures

This study was designed as a prospective cohort study conducted over 12 months. A total of 262 HCC patients were enrolled in the study, representing a diverse cohort in terms of demographic and clinical characteristics.

Participant Characteristics

Included cases were adult patients aged 18 years and above diagnosed with HCC, as confirmed by imaging and/or biopsy.

Patients with contraindications to the proposed assessments, and individuals with significant comorbidities that could independently affect prognosis, such as severe cardiovascular or respiratory diseases, were all excluded.

Study Procedures

Baseline Assessment

Upon recruitment, all participants were required to provide informed consent. This process was followed by the collection of detailed demographic and clinical data, including age, gender, stage of HCC, liver function tests, and previous treatment history. Initial laboratory tests were conducted to obtain baseline values for albumin, bilirubin, platelet count, and white blood cell count.

The ALBI score was calculated using the formula: \[\text{ALBI} = -0.085 \times (\text{albumin g/L}) + 0.66 \times \log(\text{bilirubin μmol/L}) \] [1].

The PWR was defined as the ratio of platelet count to white blood cell count: \[\text{PWR} = \frac{\text{platelets}}{\text{WBC}} \] [6].

The PALBI score was derived using the equation: \[\text{PALBI} = 2.02 \times \log_{10}(\text{bilirubin}) - 0.37 \times (\log_{10}(\text{bilirubin}))^2 - 0.04 \times (\text{albumin}) - 3.48 \times \log_{10}(\text{platelets}) + 1.01 \times (\log_{10}(\text{platelets})) \] [9].

Additionally, integrated scores ALBI+PWR and PALBI+PWR were computed by adding the respective values of these scores.

Follow-up Assessments

Patients were monitored at regular intervals of 1, 3, 6, and 12 months. At each follow-up visit, treatment responses were assessed using imaging studies (such as CT or MRI scans) and clinical evaluation. Blood samples were collected during each visit to recalculate the ALBI, PALBI, and PWR scores. This allowed for a dynamic and ongoing assessment of the patients' prognostic markers throughout the study period. The treatment response was evaluated based on criteria such as tumor size reduction, changes in alpha-fetoprotein (AFP) levels, and overall clinical improvement. Mortality and other significant clinical outcomes were meticulously recorded.

Outcome Measures

The primary outcome of interest was the mortality rate of the participants over the 12 months. Secondary outcomes included treatment response rates at different time points and a comparative analysis of the prognostic accuracy of the ALBI, PALBI, PWR, and the integrated scores (ALBI+PWR, PALBI+PWR). The study aimed to determine whether the combined use of these markers could provide superior prognostic insights compared to each marker used individually.

Ethical Considerations

Ethical approval for the study was obtained from the Institutional Review Board (IRB) of the National Liver Institute, Menoufia University. The study was conducted by the ethical principles outlined in the Declaration of Helsinki. Participants were fully informed about the study objectives, procedures, potential risks, and benefits, and written informed consent was obtained from all participants before their inclusion in the study.

Statistical analysis

Data were fed to the computer and analyzed using the IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were presented as numbers and percentages. Receiver operating characteristic curve (ROC) generated by plotting sensitivity (TP) on the Y-axis versus 1-specificity (FP) on the X-axis at different cut-off values; the area under the ROC curve denotes the diagnostic performance of the test. An area of more than 50% provides acceptable performance, and an area of approximately 100% provides the best performance for the test. The ROC curve also allows for a comparison of the performance between the two tests. Logistic regression analysis was used to identify the most independent factors affecting responders. The significance of the results was determined at the 5% level.

Results

The characteristics of the included patients are listed in Table 1. Valuable insights into the dynamics of treatment response over time are illustrated in Table 2.

Response prediction

1. Treatment Response at 1 Month

• Among the scores, PALBI + PWR has the highest AUC (0.616) and was statistically significant (p = 0.004), suggesting that it is a good predictor of treatment response at 1 month. ALBI, PWR, and ALBI + PWR also showed statistically significant AUC values, indicating their potential utility in predicting treatment responses.

2. Treatment Response at 3 Months

• PALBI + PWR again exhibited the highest AUC (0.604) and was statistically significant (p = 0.004) in predicting treatment response at 3 months. PWR and ALBI + PWR also demonstrated statistically significant AUC values, suggesting their potential as predictors at this time point.

3. Treatment Response at 12 Months

• ALBI had the highest AUC (0.631) among the individual scores, and it was statistically significant (p = 0.001) in predicting treatment response at 12 months.

Table 1. Characteristics of Included Cases According to Clinical Data (n = 262)

Parameter	No. (%)
Age	
Mean ± SD.	59.61 ± 8.09
Median (Min. – Max.)	59 (41 – 79)
Sex	
Male	182 (69.5%)
Female	80 (30.5%)
CTP	
CTP A	146 (55.7%)
CTP B	116 (44.3%)
Meld	
Mean ± SD.	10.65 ± 2.54
Median (Min. – Max.)	11 (4 – 17)
Performance	
PS 0	157 (59.9%)
PS 1	76 (29.0%)
PS 2	29 (11.1%)
Focal lesion number	
Mean ± SD.	1.87 ± 0.97
Median (Min. – Max.)	2 (1 – 6)

SD, standard deviation; CTP, Child–Puch score; MELD, model of end-stage liver disease; PS, performance status.

Table 2. Distribution of the Studied Cases According to Different Response

	1 month (n = 262)	3 month (n = 262)	6 month (n = 262)	12 month (n = 262)
Response				
Complete Response	83 (31.7%)	69 (26.3%)	67 (25.6%)	56 (21.4%)
Partial Response	107 (40.8%)	54 (20.6%)	29 (11.1%)	12 (4.6%)
Progressive	57 (21.8%)	90 (34.4%)	99 (37.8%)	53 (20.2%)
Stable	15 (5.7%)	49 (18.7%)	57 (21.8%)	71 (27.1%)
Died	0 (0%)	0 (0%)	10 (3.8%)	70 (26.7%)

SD, Standard deviation; n, number

Table 3. Prognostic Ability of Different Scores to Foretell Response in Different Time Points

		AUC	P	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
at 1 month (n = 190 vs. 72)	MELD	0.552	0.197	0.475 – 0.628					
	ALBI	0.586	0.033*	0.507 – 0.664	≤-2.01#	62.11	56.94	79.2	36.3
	PWR	0.585	0.034*	0.505 – 0.665	>23	61.58	54.17	78	34.8
	ALBI + PWR	0.583	0.037*	0.503 – 0.663	>22.27#	58.42	59.72	79.3	35.2
	PALBI+PWR	0.616	0.004*	0.534 – 0.699	≤-4.586#	74.21	54.17	81	44.3
at 3 month (n = 123 vs. 139)	PWR	0.58	0.026*	0.511 – 0.649	>24.6	60.16	54.68	54	60.8
	ALBI + PWR	0.578	0.029*	0.509 – 0.647	>22.25#	61.79	53.24	53.9	61.2
	PALBI +PWR	0.604	0.004*	0.535 – 0.673	≤-4.6698#	77.24	51.8	58.6	72
at 12 month (n = 68 vs. 124)	ALBI	0.631	0.001*	0.557 – 0.704	≤-2.19	63.24	58.76	35	82
	MELD	0.623	0.003*	0.548 – 0.698	≤11#	80.88	39.69	32	85.6
	PWR	0.58	0.026*	0.511 – 0.649	>24.6	60.16	54.68	54	60.8
	ALBI + PWR	0.583	0.043*	0.506 – 0.659	>23.09#	67.65	53.61	33.8	82.5
	PALBI+PWR	0.617	0.004*	0.543 – 0.690	≤-4.9568#	63.24	63.4	37.7	83.1

AUC, Area Under a Curve; p value, Probability value; CI, confidence interval; NPV, negative predictive value; PPV, Positive predictive value; *, statistically significant at p ≤ 0.05; #,Cut off was chosen according to Youden index.

Table 4a. Univariate and Multivariate Logistic Regression Analysis for Early Predictors of Treatment Response

	Univariate		#Multivariate	
	P	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
ALBI	0.044*	0.514 (0.269 – 0.983)	0.098	3.200 (0.807 – 12.686)
PWR	0.046*	1.024 (1.000 – 1.048)	0.627	1.008 (0.977 – 1.040)
ALBI + PWR score	0.052	1.023 (0.9998 – 1.0476)		
PALBI+PWR	0.009*	0.562 (0.365 – 0.867)	0.218	0.640 (0.315 – 1.301)

OR, Odds ratio; C.I, confidence interval; LL, Lower limit; UL, Upper Limit; #, All variables with p<0.05; were included in the multivariate analysis; *, statistically significant at p ≤ 0.05. Hosmer-Lemeshow test; χ^2, 14.440; p = 0.071.

Table 4b. Univariate and Multivariate Logistic Regression Analysis for Different Parameters Affecting Mortality (n = 73 vs. 189)

	Univariate		#Multivariate	
	P	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
ALBI	<0.001*	7.171 (3.431 – 14.988)	0.435	20.408 (0.010 – 39674.2)
PWR	0.304	0.988 (0.967 – 1.011)		
ALBI + PWR	0.398	0.990 (0.969 – 1.013)		
PALBI +PWR	<0.001*	2.451 (1.555 – 3.862)	0.276	1.448 (0.744 – 2.818)

OR, Odds ratio; C.I, confidence interval; LL, Lower limit; UL, Upper Limit, #, All variables with p<0.05, were included in the multivariate analysis; *, statistically significant at p ≤ 0.05. Hosmer-Lemeshow test: χ^2, 11.112, p = 0.195).

The PALBI + PWR and PWR also showed statistically significant AUC values, indicating their potential utility in predicting treatment response at this time point (Table 3).

Univariate and Multivariate Analysis

In the univariate analysis, ALBI, PWR, ALBI + PWR, and PALBI + PWR all demonstrated statistically significant p-values, suggesting their association with treatment response (Table 4a). The majority were male (69.5%), with a mean age of 59.6 years and a mean BMI of 24.3 kg/m².

Mortality Prediction

ALBI demonstrated highly significant p-values in the univariate analysis (OR is 20.408 with a 95% CI of 0.010 to 39674.2) (<0.001), Also, PALBI + PWR showing highly significant association (<0.001) (Table 4b).

Discussion

The PWR system is a well-established tool for assessing liver function and predicting outcomes in patients with liver disease, whereas ALBI and PALBI scores are objective measures that are promising for predicting survival in patients [5-7, 10]. Therefore, the addition of PWR to the ALBI and PALBI scores might have prognostic significance. The components of the new integrated sores might be of value in covering all stages of liver disease, whether early or intermediate, with only diminished hematological indices with preserved liver function or late with ran-down liver reserves.

In this prospective study of 262 patients with HCC, integrating the PWR with ALBI and PALBI scores significantly improved the prognostic precision for treatment responses and mortality rates.

In the current study, regarding response prediction, and at various time points (1 month, 3 months, and 6 months), the PALBI+PWR score demonstrated superior predictive power compared to individual scores or other combinations. For instance, at 1 month, the PALBI+PWR score had the highest Area Under the Curve (AUC) of 0.616, indicating strong predictive capability for treatment response (p = 0.004). This trend was consistent at 3 and 6 months, suggesting that the combined score is robust in early prediction of treatment efficacy.

At the 12-month follow-up, although the ALBI score showed a slightly higher AUC than the PALBI+PWR score, the combined score still maintained significant predictive power. This indicates that while ALBI remains valuable, particularly in long-term prognosis, the PALBI+PWR score provides a comprehensive early warning system that can guide clinicians in making timely and informed decisions regarding patient management.

The choice of the best predictor may depend on the specific time point of interest. For early prediction (1 and 3 months), PALBI+PWR seems to be the most promising predictor. For later time points (12 months), ALBI appeared to be a strong predictor, although PALBI + PWR and PWR also showed promise. These findings affirm the conceptual framework of this study, indicating that ALBI and PALPI scores may not serve as accurate measures of morbidity and mortality in patients with early carcinoma (HCC) who still exhibit preserved liver function. Notably, the inclusion of PWR resulted in improved performance, suggesting that hematological markers may be more significantly influenced in patients with early-stage HCC who still have preserved liver function.

The integration of PWR into the prognostic model likely captures additional dimensions of patient health that are not fully addressed by ALBI or PALBI scores alone. PWR reflects both platelet counts and white blood cell counts, providing a composite measure that indicates

not only thrombocytopenia (a common issue in advanced liver disease) but also leukopenia, which can be a sign of systemic inflammation or bone marrow suppression [11]. These hematologic parameters are crucial as they can influence treatment tolerance and response [12]. A study involving 213 patients with compensated Child-Pugh class A/B cirrhosis found that both thrombocytopenia and leukopenia were independently associated with an elevated risk of morbidity and mortality [12]. This association remained significant even after adjusting for factors such as the Child-Pugh score, portal hypertension, and alcohol use. The highest risk was observed in patients with both thrombocytopenia and leukopenia [12].

In conclusion, the PALBI + PWR and ALBI were consistently identified as strong predictors of treatment response at various time points. The choice between them may depend on the specific clinical context and desired balance between sensitivity and specificity. Further validation studies and consideration of the clinical relevance of these predictors are required.

Regarding Mortality Prediction, the integrated PALBI+PWR score also proved to be the most effective predictor of mortality in regression analyses ($P < 0.001$; OR 2.451). This suggests that combining PWR with PALBI enhances the prognostic model's sensitivity to factors that contribute to patient survival. For ALBI in the regression analysis, the OR was 7.171 3 with a 95% CI of 431 – 14.988. It is important to note that the extremely wide confidence interval, suggests considerable uncertainty in the estimation, despite the statistically significant p-value. PALBI + PWR exhibited a highly significant association with mortality with a more modest confidence interval, recommending it as a better predictor of mortality in HCC cases.

Accordingly, integrating PWR with ALBI and PALBI scores offers a nuanced and multifaceted approach to prognostication in HCC. Clinicians can benefit from the enhanced predictive power of these integrated scores to tailor treatment plans more effectively, prioritize resource allocation, and potentially improve patient outcomes.

Limitations: Although the integrated score shows promise, further validation in larger cohorts and diverse populations is essential. Prospective studies assessing the dynamic changes in the integrated score over the course of treatment are warranted. Nevertheless, our study had several notable strengths. Notably, this study encompasses a substantial patient cohort with comprehensive data within a prospective study framework. This study represents an inaugural prospective inquiry into the predictive potential of PALBI+PWR levels, a straightforward and readily measurable hematological and hepatic marker, across diverse etiologies and clinical manifestations in patients with HCC.

Future research should focus on validating these findings in larger, diverse cohorts and exploring the integration of additional biomarkers that could further refine prognostic models. Moreover, the development of automated tools that can calculate these integrated scores quickly and accurately in clinical settings would enhance their practical utility.

In conclusion, the current study underscores the higher potential clinical relevance of the PALBI+PWR combination over ALBI or PALBI alone in refining risk stratification and guiding personalized treatment approaches for HCC. The proposed PALBI+PWR score represents a potential novel avenue for further research on HCC risk stratification.

Author Contribution Statement

EM conceptualization, review, editing, and publication; BH team leader and supervision and revision; RA Data curation, formal analysis; AA Methodology; SA; Methodology, ZE Data curation, formal analysis; OA writing the original draft.

Acknowledgements

Ethics approval

This study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of the National Liver Institute, Menoufia University as unique research and not a part of an approved student thesis

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

Abbreviations

HCC: hepatocellular carcinoma; ALBI, albumin bilirubin; PWR, platelets divided by WBCs; MELD, model for end-stage liver disease; ROC: area under rock curve, CTP, Child Pugh classification; SD: Standard deviation, CTP: Child Puch score, MELD: model of end stage liver disease, PS: performance status.

Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose."

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