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Day-to-day variation in physiological network connectivity predicts outcomes in decompensated cirrhosis

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Abstract

Cirrhosis is a complex multisystem disease in which physiological network disruption is associated with adverse outcomes. Network mapping of routine biomarkers predicts mortality independently of established prognostic scores, but previous studies have assessed networks only at a single time point. We aimed to determine whether day-to-day network stability and variation during hospitalisation are associated with outcomes in decompensated cirrhosis.

In this sub-study of the multicentre ATTIRE trial, daily albumin, bilirubin, creatinine, CRP and WCC measurements from 777 patients were analysed using parenclitic network mapping, with standard-care survivors as the reference population. Mean parenclitic deviation and day-to-day variation in network deviations during the first week of hospitalisation were compared between 15-day survivors and non-survivors and tested for associations with mortality after adjustment for MELD and age.

Three network connections were identified. Mean parenclitic deviation was greater in non-survivors along the CRP–WCC ($P = 9\times10^{-5}$) and WCC–bilirubin ($P = 7\times10^{-7}$) axes. Day-to-day variation was also greater in non-survivors (mean absolute successive difference: $P = 3\times10^{-6}$; $P = 8\times10^{-12}$, respectively) and predicted survival independently of mean deviation, MELD and age.

Temporal network dynamics provide prognostic information beyond static measurements, highlighting dysregulated immune–hepatic interactions and reduced physiological network stability as determinants of survival in decompensated cirrhosis.

Introduction

Advanced chronic liver disease is divided into compensated and decompensated cirrhosis, with the latter associated with high mortality especially with co-existent multiple organ dysfunction (acute-on-chronic liver failure) (Ginès et al., 2021). The multi-organ involvement observed in decompensated cirrhosis highlights the importance of the liver as a major hub within the physiological system, whereby liver failure can lead to disruption of other physiological subsystems, including coagulation, metabolic, immune, neural, cardiovascular, renal and circadian systems (Engelmann et al., 2021; Lewis et al., 2025).

Given this multisystem involvement, recent research has suggested applying a complex-systems approach to the study of cirrhosis (Oyelade et al., 2024). This approach enables network mapping of the interactions between different physiological subsystems, rather than studying each system in isolation. The potential value of a network-based approach is supported by observations showing that physiological network maps can predict clinical outcomes, including survival, independently of established clinical prognostic models such as the model for end-stage liver disease score (MELD) (Tan et al., 2020; Zhang et al., 2022; Oyelade et al., 2023).

Prognostication in patients with decompensated cirrhosis is clinically important, as it can help guide the equitable allocation of organs for transplantation (the only effective treatment) and may also facilitate

the timely involvement of palliative care (Ge et al., 2022; Rogal et al., 2022).

Although considering relationships between physiological markers through network mapping is conceptually well-suited to a complex multisystem disease, an important methodological limitation has been the ability to construct individualised physiological networks using routine clinical and/or laboratory data available for patients with decompensated cirrhosis. In recent years, progress has been made in addressing this limitation through the development of network approaches based on physiological time-series data or routine biomarkers, including the application of parenclitic networks (Oyelade et al., 2024; Ito et al., 2025; Feng et al., 2026). In critically ill patients including those with decompensated cirrhosis, the number and strength of correlations between physiological biomarkers falls, and this predicts death independent of conventional severity scores (Asada et al., 2016; Tan et al., 2020). Parenclitic network analysis applies the approach to the individual patient. The expected relationship between each pair of biomarkers is derived from a reference population, and the distance of a patient from that relationship becomes the weight of a network edge (Zanin et al., 2014). In cirrhosis, parenclitic deviation at hospital admission predicts survival independent of MELD and Child-Turcotte-Pugh (Zhang et al., 2022), and in the ATTIRE (Albumin To prevent Infection in chronic liver failure) clinical trial it predicted 6-month mortality and identified a subset of patients who did not benefit from targeted albumin therapy (Oyelade et al., 2023).

Patients with decompensated cirrhosis are frequently hospitalised because of acute complications, including ascites, hepatic encephalopathy, variceal bleeding, bacterial infections, and acute kidney injury. Both previous studies that applied parenclitic networks in cirrhosis mapped the physiological network at a single time point (i.e. at the time of hospital admission), and both identified this as an important limitation (Zhang et al., 2022; Oyelade et al., 2023). Thus, while the prognostic value of physiological network mapping at the time of admission has been demonstrated, little is known about day-to-day variation in physiological networks during hospitalisation.

This is clinically relevant because patients undergo multiple treatments during their hospital stay, which may alter physiological interactions and organ-system connectivity. Tracking these changes may therefore provide additional information about the patient's evolving physiological state and response to treatment. Importantly, it remains unclear how stable networks derived using the parenclitic method are over time and how hospitalisation and treatment affect physiological network connectivity.

The present study aimed to address these questions using data obtained from the ATTIRE trial (China et al., 2021). Biomarkers were measured daily during the treatment period of the trial, allowing each patient's physiological network to be followed longitudinally over the first week of hospital admission. We therefore assessed the day-to-day stability of parenclitic network deviation and investigated whether changes in network deviation over time were associated with clinical outcomes in hospitalised patients with decompensated cirrhosis.

Methods

Patients and follow-up

This is a sub-study and extension of the analysis of data obtained from the ATTIRE trial, a multicentre randomised trial of targeted albumin therapy versus standard care in 777 patients hospitalised with decompensated cirrhosis across 35 hospitals in England, Wales and Scotland (2016–2019) (China et al., 2021). The trial found no benefit on its composite primary endpoint of new infection, renal dysfunction or death between days 3 and 15 of treatment, and there were no differences in baseline characteristics between treatment groups (China et al., 2021). Patients were grouped as survivors and non-survivors based on survival status during the trial's primary period (day 15), and by treatment arm (albumin or standard care).

Ethics statement

The ATTIRE trial was approved by the London–Brent Research Ethics Committee (reference 15/LO/0104) and the Medicines and Healthcare Products Regulatory Agency (reference 20363/0350/001–0001) (China et al., 2021). The trial was conducted in accordance with the principles of Good Clinical Practice and the provisions of the Declaration of Helsinki. Written informed consent was obtained from all participants with capacity. For participants lacking capacity, written informed consent was provided by an appropriate legal representative in accordance with UK clinical trials regulations (China et al., 2021).

Clinical laboratory variables

Five laboratory variables representing distinct physiological functions were recorded on each day of the treatment window (days 1–14): serum albumin, total bilirubin, serum creatinine, C-reactive protein (CRP) and white cell count (WCC). The values recorded before the treatment window were not used. Albumin and creatinine were not recorded beyond treatment day 14, so day 15 was excluded to keep the same set of days available for every connection. These cover hepatic synthetic and excretory function, renal function and systemic inflammation, and are the variables available as daily series in this trial.

Network generation in the population

The reference population is 364 patients in the standard-care group who survived the primary period (15 days). For each reference patient, all variables were averaged over all days of recording, so that the whole treatment window contributes to the reference while each patient contributes one observation. Spearman's correlation was then computed between each pair of these averages, with pair matching to correct for missing data, so that each correlation used every patient in whom both variables were recorded. An edge was formed between a pair of variables if the correlation between them was significant at a Bonferroni-corrected level ($P < 0.005$; Dunn, 1961). Edges (i.e. correlation pairs) that did not meet this threshold were excluded from the correlation network and further analysis.

Parenclitic network: deviation value computation (δ)

Parenclitic network analysis measures the deviation of each patient from the existing network of physiological interactions in a reference population. For each significantly correlated pair of variables, a regression model was constructed from the reference data by orthogonal regression. Orthogonal linear regression was used because it accounts for measurement errors in both dependent and independent variables and treats the two variables symmetrically (Ito et al., 2025; Boggs and Rogers, 1990).

The parenclitic deviation (δ) of an individual patient on a given day is the perpendicular distance of that day's pair of values from the expected line. The computed δ values were used as the weights of the connections between correlated pairs of variables for all patients on all days, so that each patient has one network per treatment day (Fig. 1).

For each patient and each connection, δ was summarised over treatment days 1–7 by its mean, requiring at least three observed days within the window. The mean parenclitic deviation describes how far the patient sits from the expected relationship over the window. This corresponds to the quantity assessed at a single time point in previous parenclitic analyses in cirrhosis (Zhang et al., 2022; Oyelade et al., 2023).

Day-to-day variation indices

Where the mean parenclitic deviation describes the distance the patient sits from the expected relationship, the day-to-day variation indices describe how much that distance changes between consecutive days. Both were computed over the same window and with the same minimum of three observed days. Writing δ_t for the deviation on day t and k for the number of observed days:

1. the mean absolute successive difference, $\mathrm{MASD} = (1/(k-1)) \Sigma |\delta_{t+1} - \delta_t|$;

2. the coefficient of variation, $\mathrm{CV} = \mathrm{SD}(\delta)/\mathrm{mean}(\delta)$.

Two indices are used because variability indices generally scale with their own mean (Monfredi et al., 2014). MASD is positively correlated with the mean parenclitic deviation, whereas the CV, being scaled by the mean, is negatively correlated with it, so the mean parenclitic deviation is included as a covariate wherever either index is tested against outcome.

Statistical analysis

Statistical analysis was performed in Python (SciPy and statsmodels), with data presented as median and interquartile range (IQR). A two-tailed P value of < 0.05 was defined as statistical significance in all analyses. Each connection was analysed separately, and the Bonferroni correction was applied across the three retained connections whenever an index was tested on each of them.

Initially, we performed a two-way analysis of variance to compare the mean parenclitic deviation and the day-to-day variation indices between the survivor and non-survivor groups, with survival status and

treatment arm as the two factors and their interaction. Indices were log-transformed before the analysis of variance to reduce skewness; medians and interquartile ranges are reported in the original units.

The indices were then tested for prognostic value by multivariable logistic regression, adjusting for the mean parenclitic deviation of the same connection, MELD and age:

$$\text{logit}(p) = \beta_0 + \beta_1 \cdot \text{MASD} + \beta_2 \cdot \text{mean } \delta + \beta_3 \cdot \text{MELD} + \beta_4 \cdot \text{age}$$

where p is the probability of death during the primary period. All predictors were standardised by subtracting the mean and dividing by the standard deviation of the sample analysed for that connection. Each odds ratio therefore describes the change in odds of death associated with a one standard deviation increase in that predictor, with the others held constant. Because the predictors are measured on different scales, this also allows their effect sizes to be compared directly. The model was refitted with the coefficient of variation in place of MASD, and again with the number of observed days added as a covariate.

The analysis was repeated against 180-day mortality using Cox proportional hazards regression with the same covariates and standardisation. Follow-up was counted from treatment day 7, and patients who died on or before day 7 were excluded, so that the indices were fixed before follow-up began.

Results

Patient characteristics at ATTIRE trial

Of 777 patients (380 albumin, 397 standard care), 63 died during the primary period (15 days). Demographic and clinical variables are shown in Table 1. Non-survivors were older and had higher MELD, creatinine, white cell count and CRP, and were more often admitted with infection, renal dysfunction or hepatic encephalopathy.

Table 1

Demographic and clinical variables in the study population. Data are median (interquartile range) unless otherwise stated. CRP, C-reactive protein; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; n, number of patients; WCC, white cell count.

Characteristic	All patients (n = 777)	Survivors (n = 714)	Non-survivors (n = 63)
Age, years	53.6 (46.7–60.7)	53.3 (46.6–60.5)	56.8 (51.6–63.2)
Male sex, n (%)	549 (71)	506 (71)	43 (68)
MELD score	19.6 (15.4–23.1)	19.1 (15.4–23.0)	22.1 (17.6–26.4)
Albumin arm, n (%)	380 (49)	350 (49)	30 (48)
Infection at baseline, n (%)	211 (27)	183 (26)	28 (44)
Reason for admission, n (%)			
Alcohol-related hepatitis	203 (26)	188 (26)	15 (24)
Ascites or jaundice	440 (57)	399 (56)	41 (65)
Infection	162 (21)	137 (19)	25 (40)
Renal dysfunction	57 (7)	42 (6)	15 (24)
Hepatic encephalopathy	149 (19)	128 (18)	21 (33)
Variceal bleed	115 (15)	105 (15)	10 (16)
Physiological variables			
Serum albumin, g/L	26 (23–30)	26 (23–30)	26 (24–28)
Creatinine, µmol/L	66 (54–87)	66 (54–85)	80 (62–120)
Bilirubin, µmol/L	96 (46–172)	96 (45–165)	117 (54–227)
C-reactive protein, mg/L	24 (12–47)	23 (11–44)	56 (21–86)
White cell count, $\times 10^9$/L	7.5 (5.3–11.2)	7.4 (5.2–10.8)	11.0 (7.5–16.2)

Population cross correlation network of the reference population

Three of the ten correlations computed in the reference group were statistically significant at the Bonferroni-corrected level: CRP–WCC ($\rho = 0.37$, $P = 9\times10^{-13}$), WCC–bilirubin ($\rho = 0.31$, $P = 1\times10^{-9}$) and albumin–bilirubin ($\rho = -0.15$, $P = 0.004$). Creatinine did not form a significant correlation with another variable and so forms no connection, as was also the case in both previous parenclitic analyses of cirrhosis (Zhang et al., 2022; Oyelade et al., 2023). Thus, these three axes (CRP–WCC, WCC–bilirubin, albumin–bilirubin) were used for calculation of parenclitic deviations for individual patients.

Parenclitic network analysis across the overall population

Parenclitic deviation along all three connections across the treatment period is shown in Fig. 1. On both connections involving WCC, non-survivors show consistently higher deviation over the treatment days: the mean δ on day 1 was 5.5 versus 3.5 for WCC–bilirubin and 5.3 versus 3.5 for CRP–WCC. Survivors remained close to their day 1 value across the two weeks, whereas non-survivors rose over the first four to six days and then remained elevated. Along the albumin–bilirubin connection, both survivor and non-survivor groups' deviations rose closely together, with both rising from around 4 on day 1 to above 6 by the end of the first week.

Parenclitic deviation indices over the first week of treatment differentiate survivors and non-survivors

To assess the effects of trial treatment, study outcome, and their interaction on parenclitic deviations, parenclitic deviation indices were compared between survivors and non-survivors and between the two trial arms (targeted albumin therapy versus standard care) using two-way ANOVA. The results are presented in Table 2.

Table 2

Results of two-way analysis of variance (ANOVA) for the effect of survival and treatment on mean parenclitic deviation (δ) and day-to-day variation of δ (mean absolute successive difference (MASD) and coefficient of variation (CV)) by connection.

Connection (axis)	Index	Survivors	Non-survivors	P, survival status	P, treatment arm	P, interaction
Albumin–bilirubin (n = 544)	Mean δ	5.41 (2.98 to 7.18)	4.37 (3.48 to 6.37)	> 0.99	**2×10^{-27}**	0.25
	MASD	1.93 (1.27 to 2.77)	2.13 (1.46 to 2.57)	0.42	**2×10^{-14}**	0.50
	CV	0.45 (0.28 to 0.65)	0.52 (0.37 to 0.63)	0.97	0.77	> 0.99
CRP–WCC (n = 612)	Mean δ	2.90 (1.68 to 4.43)	3.53 (2.47 to 6.57)	**9×10^{-5}**	> 0.99	> 0.99
	MASD	1.00 (0.63 to 1.52)	1.93 (1.17 to 2.78)	**3×10^{-6}**	0.46	> 0.99
	CV	0.44 (0.23 to 0.67)	0.53 (0.35 to 0.69)	0.22	0.32	> 0.99
WCC–bilirubin (n = 691)	Mean δ	3.13 (1.74 to 4.60)	4.87 (2.66 to 7.92)	**7×10^{-7}**	> 0.99	> 0.99
	MASD	0.95 (0.60 to 1.47)	2.01 (1.19 to 3.89)	**8×10^{-12}**	> 0.99	> 0.99
	CV	0.41 (0.19 to 0.66)	0.51 (0.33 to 0.71)	**0.027**	0.63	> 0.99

Along the CRP–WCC and WCC–bilirubin axes, both the mean parenclitic deviation and MASD were significantly higher in non-survivors than in survivors. The coefficient of variation (CV) was also significantly higher in non-survivors along the WCC–bilirubin axis (Table 2). For both the CRP–WCC and WCC–bilirubin axes, there were no significant differences between the treatment arms and no significant interactions between survival status and treatment arm.

Along the albumin–bilirubin axis, none of the indices differed significantly according to survival status. In contrast, treatment arm had a significant effect on both mean deviation and MASD, as expected given the effect of targeted albumin infusion on serum albumin concentrations (Supplementary Figure S1).

Independent prognostic values of day-to-day variation indices to predict survival during the treatment period

Multivariable logistic regression was used to test whether the day-to-day variation indices (i.e. MASD and CV) predicted survival during the primary period after adjusting for MELD, age and the mean parenclitic deviation along the same connection (Table 3, Fig. 3). To ensure comparability between the predictors, all predictors were standardised by subtracting the mean and dividing by the standard deviation of the sample analysed for that connection. Along the WCC–bilirubin axis, greater MASD was associated with increased odds of death (odds ratio 1.42 per standard deviation, 95% CI 1.11 to 1.83). The CV predicted survival along both axes involving WCC, with odds ratios for death of 1.51 (1.17 to 1.96) for WCC–bilirubin and 1.49 (1.12 to 1.97) for CRP–WCC. Neither index along the albumin–bilirubin axis was predictive. Because non-survivors are recorded for fewer days, the models were refitted with the number of observed days added; this was not associated with death along any connection and left the odds ratios unchanged.

Table 3

Prognostic value of day-to-day variation indices (mean absolute successive difference (MASD) and coefficient of variation (CV)) in parenclitic deviation independent of mean parenclitic deviation (δ), Model for End-Stage Liver Disease (MELD), and age.

Connection	**n (deaths)**	**MASD**	**Mean δ**	**MELD**	**Age**	**Corrected P (MASD)**
Albumin–bilirubin	535 (46)	1.06 (0.76 to 1.49), P = 0.72	0.85 (0.61 to 1.20), P = 0.36	**1.48 (1.11 to 1.96), P = 0.007**	**1.79 (1.31 to 2.45), P = 3×10^{-4}**	> 0.99
CRP–WCC	603 (53)	1.15 (0.89 to 1.47), P = 0.29	**1.46 (1.13 to 1.89), P = 0.003**	**1.73 (1.31 to 2.29), P = 1×10^{-4}**	**1.88 (1.38 to 2.55), P = 6×10^{-5}**	0.87
WCC–bilirubin	681 (60)	**1.42 (1.11 to 1.83), P = 0.006**	**1.40 (1.08 to 1.83), P = 0.012**	**1.49 (1.14 to 1.94), P = 0.003**	**1.73 (1.28 to 2.32), P = 3×10^{-4}**	**0.017**
Connection	n (deaths)	CV	Mean δ	MELD	Age	Corrected P (CV)
Albumin–bilirubin	535 (46)	1.00 (0.70 to 1.43), P > 0.99	0.87 (0.61 to 1.25), P = 0.47	**1.48 (1.11 to 1.96), P = 0.007**	**1.79 (1.31 to 2.45), P = 3×10^{-4}**	> 0.99
CRP–WCC	603 (53)	**1.49 (1.12 to 1.97), P = 0.006**	**1.70 (1.36 to 2.13), P = 3×10^{-6}**	**1.69 (1.28 to 2.24), P = 2×10^{-4}**	**1.90 (1.39 to 2.61), P = 6×10^{-5}**	**0.019**
WCC–bilirubin	681 (60)	**1.51 (1.17 to 1.96), P = 0.002**	**1.86 (1.49 to 2.32), P = 4×10^{-8}**	**1.49 (1.14 to 1.94), P = 0.004**	**1.75 (1.30 to 2.36), P = 2×10^{-4}**	**0.005**

Cox proportional hazards regression was used to test whether these associations extended to 180-day mortality, with follow-up counted from treatment day 7 (Supplementary Table S1). Along both axes involving WCC, greater MASD was associated with increased hazard of death: hazard ratio 1.21 per standard deviation (95% CI 1.07 to 1.37) for WCC–bilirubin and 1.20 (1.04 to 1.38) for CRP–WCC. The

CV was associated with 180-day mortality along the CRP–WCC axis (1.21, 1.05 to 1.41). Along the WCC–bilirubin axis the CV hazard ratio was in the same direction but did not remain significant after correction for the three connections (1.18, 1.03 to 1.35) (Supplementary Figure S2). Neither index along the albumin–bilirubin axis was associated with 180-day mortality.

Discussion

The present study aimed to assess the day-to-day stability and prognostic value of parenclitic network deviations in hospitalised patients with decompensated cirrhosis. Our analysis of daily clinical data shows that patients who died differed from those who survived not only in how far their physiological variables sat from the expected relationship, but in how much that difference changed from one day to the next. The difference was confined to the two axes involving the white cell count, and day-to-day variation along both predicted survival independent of the mean parenclitic deviation, MELD and age (Table 3, Fig. 3).

Increased parenclitic deviation within a network reflects greater deviation from the reference relationship between variables and can be interpreted as reduced connectivity between physiological systems (Ito et al., 2025). Increased parenclitic deviation along axes such as CRP–WCC and WCC–bilirubin has previously been reported in non-survivors with cirrhosis, consistent with disruption of the physiological network (Oyelade et al., 2023). However, previous studies assessed these networks at only a single, static time point. Our current findings are consistent with these earlier observations but add a novel dimension related to the concept of *network stability*. We showed that day-to-day variation along the two network axes were substantially lower in survivors than in non-survivors. This suggests that, during hospitalisation for decompensated cirrhosis, patients who do not survive have less stable physiological networks than those who survive.

This observation is particularly interesting in the context of numerous seminal studies across different complex systems demonstrating that network stability and structural resilience are critical to maintaining system function (May, 1972; Buldyrev et al., 2010; Gao et al., 2016). Across fields as diverse as computer science and ecology, loss of network stability can increase vulnerability to tipping points and cascading failures, potentially leading to system-wide dysfunction (Gao et al., 2016). More broadly, complex-systems research suggests that dysfunction can emerge when network coherence deteriorates, information flow becomes disrupted, and interactions between system components can no longer maintain overall stability (Mostashari, 2025). Such concepts are relevant to critical illness, in which progressive disruption of physiological interactions may contribute to cascading multiorgan dysfunction, as observed in sepsis (Morandotti et al., 2025a) and, in the context of the present study, decompensated cirrhosis.

Physiological network mapping is an emerging field (Bashan et al., 2012; Ivanov et al., 2021). However, relatively few studies have investigated the day-to-day dynamics of physiological networks in complex diseases. Our findings therefore provide empirical evidence for an association between physiological

network stability and survival. Although parenclitic network mapping provides a suitable approach for assessing network relationships using routinely available biomarkers, other methodologies can also be used to investigate physiological network dynamics (Bottaro et al., 2020; Morandotti et al., 2025b). For example, heart rate variability (HRV), a measure of cardiac autonomic regulation, is consistently associated with adverse outcomes in cirrhosis (Mani et al., 2009; Jansen et al., 2019; Oyelade et al., 2021; Abid et al., 2022). However, less is known about the prognostic value of day-to-day variation in HRV (Jansen et al., 2019), and HRV alone cannot capture interactions across multiple physiological systems as assessed by parenclitic network mapping.

While the methodology used in this study was guided by an integrated, network-based approach to physiological systems, the study was not designed to explore the mechanisms that may contribute to death or survival following hospitalisation for decompensated cirrhosis. Nevertheless, given that the principal nodes identified in our network analysis, particularly CRP and WCC, are mechanistically linked through the systemic inflammatory response, some cautious mechanistic interpretation of these findings can be made. WCC and CRP are two routinely measured markers of the systemic inflammatory response, and the relationship and coordination between these inflammatory markers have been investigated in previous studies. At baseline, the deviation along the CRP–WCC axis predicted 6-month survival independent of MELD and age, whereas either marker considered alone is a poor prognostic indicator in cirrhosis (Oyelade et al., 2023; Pieri et al., 2014). The earlier analysis measured this axis once; whereas we find that its day-to-day variation over the first week predicts death independently of the mean parenclitic deviation.

The WCC–bilirubin axis behaved similarly and carried the stronger signal. Deviation at baseline along this axis was also independently prognostic in the earlier analysis (Oyelade et al., 2023). CRP is synthesised by hepatocytes, and bilirubin reflects hepatic excretory function, so both axes describe the relationship between the inflammatory response and the liver's capacity to respond to it. Increasing day-to-day variation in that relationship may therefore mark the point at which the inflammatory demand placed on the liver exceeds what it can meet.

These findings support the hypothesis that a dysregulated innate immune response is a key driver of mortality in decompensated cirrhosis. Systemic inflammation, rather than failure of any single organ, determines the course a patient takes after acute decompensation (Trebicka et al., 2020; Moreau et al., 2013). A dysregulated innate immune response of this kind would be expected to show itself not as a steady departure from expected physiology, but as a failure to hold homeostasis, in which fluctuations in the internal environment are no longer returned to their usual state during the hospitalisation period. The response itself may also be impaired rather than simply excessive, since immune paresis has been described in decompensated cirrhosis (O'Brien et al., 2014).

Targeted albumin altered neither the network nor its relationship with survival, which is the network-level counterpart of the trial's overall null result, supportive of no anti-inflammatory effect for albumin (China et al., 2021). This differs from the earlier analysis of these patients, in which network state identified

those who did not benefit from albumin (Oyelade et al., 2023); that analysis used 6-month survival and was based on the network before treatment began, whereas the current study is based on the days during which albumin was being given. Death was counted during the trial's primary treatment period (days 3–15) rather than at 6 or 12 months as in the earlier parenclitic studies of cirrhosis, so there were fewer deaths and the multivariable models are correspondingly less powered. Because the indices are computed over the same period in which death is counted, early variation cannot be entirely separated from imminent death.

To address this, the analysis was repeated against 180-day mortality with follow-up beginning at treatment day 7, so that the indices were fixed before follow-up began. Day-to-day variation along both axes involving WCC remained associated with mortality, although less strongly than over the treatment period. This is expected when a single week's measurement is used to predict an outcome six months away. The persistence of this association indicates that day-to-day variation in parenclitic deviation during the first week is not merely a concurrent marker of the process of dying but carries prognostic information about the months after admission. This is clinically relevant, as the first week of admission is when daily blood tests are routinely available and decisions on escalation of care, transplantation referral and palliative care are often made (Rogal et al., 2022). A further limitation is that only three connections were retained for parenclitic network analysis, fewer than in earlier studies.

The independence of the network indices identified in this study supports the concept that current prognostic models for cirrhosis could potentially be improved (Ge et al., 2022; Oyelade et al., 2024). Established prognostic scores, such as MELD and Child-Turcotte-Pugh, summarise a small number of clinical and biochemical variables, typically assessed at a single time point, and largely treat these variables independently (Pugh et al., 1973; Kamath et al., 2001; Torp et al., 2026). Such approaches do not capture the interactions between physiological and organ systems, which may become increasingly disrupted as liver disease progresses. An important future implication of the present study is therefore the potential for dynamic physiological network indices to complement established prognostic models in decompensated cirrhosis. However, their incremental prognostic value and clinical utility will require validation in independent patient cohorts.

In summary, day-to-day variation in the coordination between the white cell count and hepatic markers predicts death in decompensated cirrhosis independent of MELD and age. The axes involved are those already implicated in these patients and following them over time adds prognostic information that a single measurement cannot provide. This supports a central role for the dysregulated innate immune response in driving mortality after decompensation, and identifies the day-to-day variation of that response, rather than its mean deviation alone, as a potential marker of it. These findings provide empirical evidence that the stability of the physiological network in decompensated cirrhosis plays a role in survival.

Declarations

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Potential competing interests

None to report.

Author Contribution

Y.V., T.O., and A.R.M. contributed to the conceptualization. A.O. contributed to clinical data collection. Y.V. contributed to the formal analysis and software development. A.R.M. contributed to the supervision. Y.V., T.O., A.R.M., and A.O., contributed to the writing—review and editing. All authors contributed to the article and approved the submitted version.

Data Availability

Data are available upon request from the corresponding author.

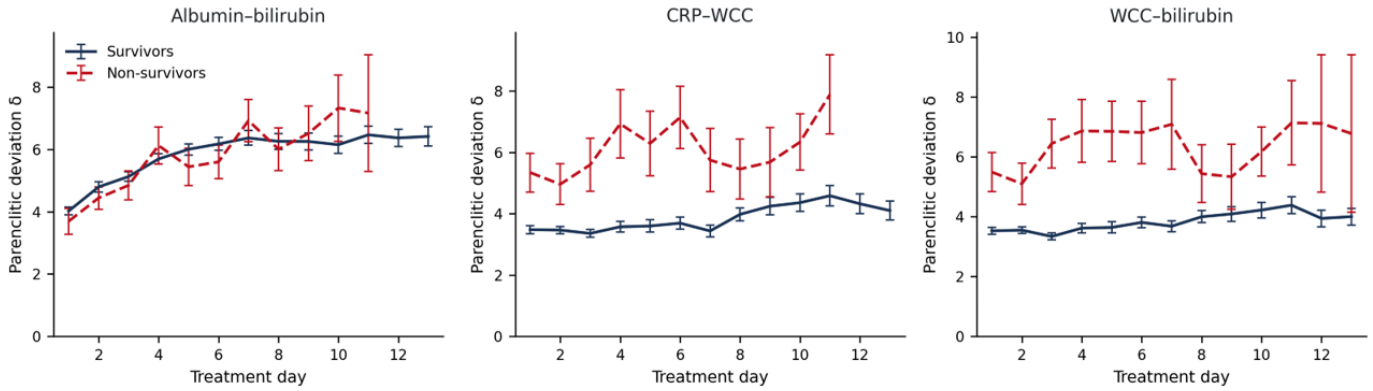
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Figures



Treatment day	1	2	3	4	5	6	7	8	9	10	11	12	13
Albumin–bilirubin													
Survivors	618	485	427	386	335	309	276	237	192	163	175	166	155
Non-survivors	55	54	43	38	30	28	23	21	19	15	10	9	4
CRP–WCC													
Survivors	624	523	432	438	383	348	313	278	221	193	188	188	167
Non-survivors	57	50	50	38	31	31	28	22	22	19	15	8	8
WCC–bilirubin													
Survivors	709	591	517	492	445	400	362	319	260	211	215	215	196
Non-survivors	63	52	59	44	39	35	31	25	25	21	17	12	10

Figure 1

Parenclitic deviation over the treatment period. *Points are the mean parenclitic deviation δ on each treatment day in survivors (navy, solid) and non-survivors (red, dashed); error bars are ± 1 standard error of that day's mean. Days on which fewer than 10 patients contributed a measurement are omitted. The table beneath the panel gives the number of patients contributing a measurement on each treatment day.* CRP, C-reactive protein; WCC, white cell count; δ, parenclitic deviation.

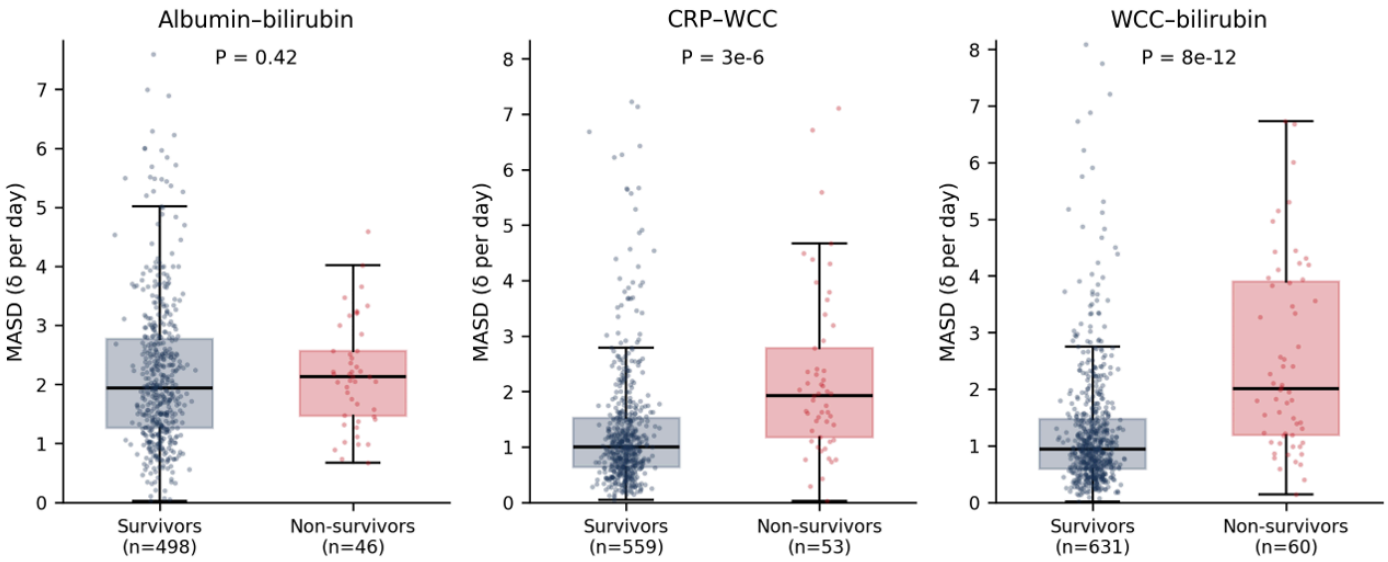


Figure 2

Day-to-day variation in parenclitic deviation in survivors and non-survivors. *The index is the mean absolute successive difference (MASD), the average change in parenclitic deviation (δ) between consecutive recorded days over treatment days 1–7, expressed in δ per day. Boxes show the median and interquartile range and the whiskers extend to 1.5 times the interquartile range; each point is one patient. The P value above each panel is the survival status term from the two-way analysis of variance (ANOVA) in Table 2, Bonferroni-corrected across the three connections.*

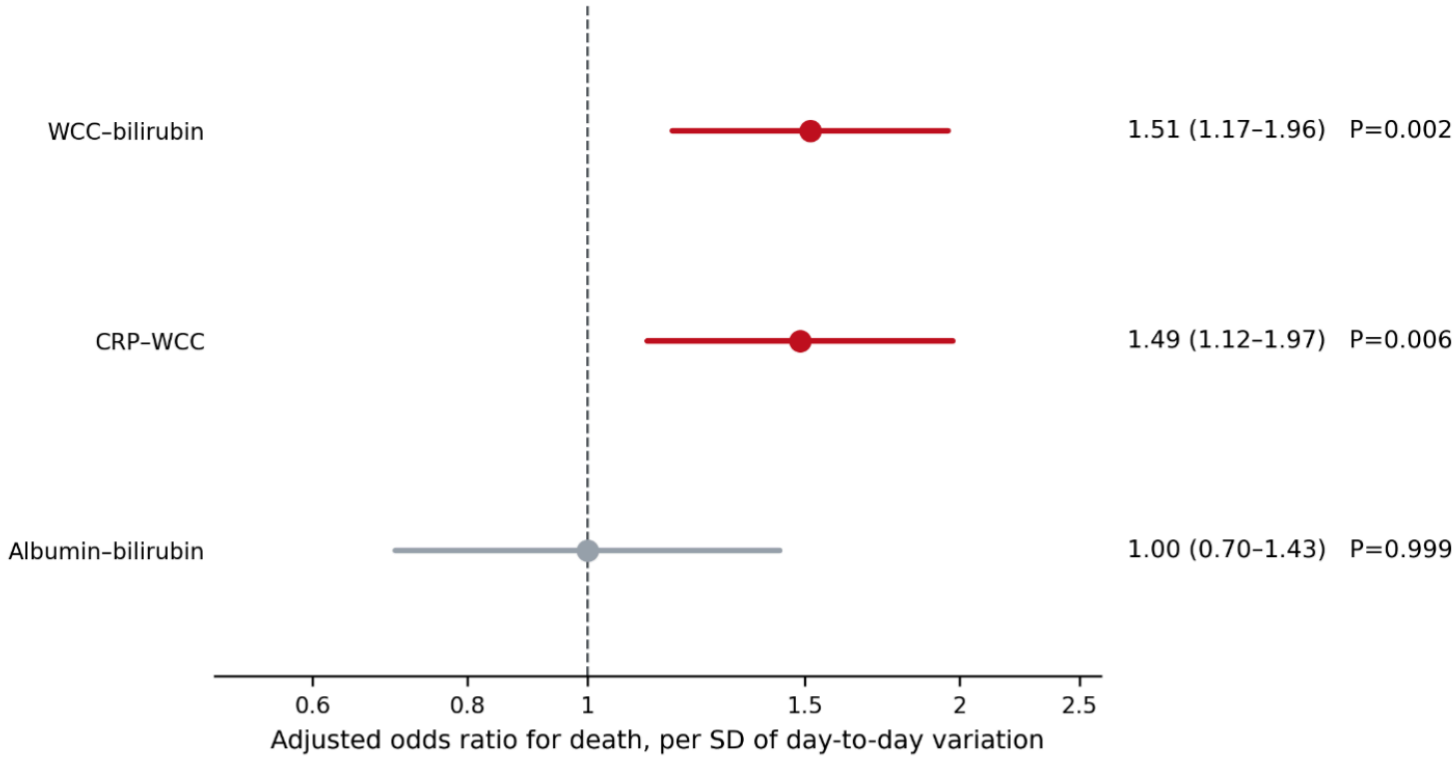


Figure 3

Adjusted odds ratios for death by connection. *Each point is the odds ratio for a one standard deviation increase in the coefficient of variation (CV) of parenclitic deviation (δ) over treatment days 1–7, with bars showing the 95% confidence interval. The odds ratios are taken from the multivariable logistic regression reported in Table 3, in which each connection was modelled separately with the CV, the mean parenclitic deviation along the same connection, Model for End-Stage Liver Disease (MELD) and age as predictors.*

Supplementary Files

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