

C3 and C4 complement consumption patterns as predictors of haemolysis severity in Iraqi autoimmune haemolytic anaemia patients: a study employing a multimarker integration approach

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Autoimmune haemolytic anaemia (AIHA) is a clinically heterogeneous disorder characterized by an immune system-mediated destruction of erythrocytes, primarily driven by autoantibodies and frequently amplified by complement activation. Although conventional laboratory parameters such as haemoglobin, lactate dehydrogenase (LDH), bilirubin, and haptoglobin levels remain essential for assessing an haemolysis, they do not adequately capture the underlying immunopathological mechanisms that influence disease severity. Increasing attention has therefore been directed toward the complement system (particularly its classical pathway) as a key mediator of erythrocyte destruction and a potential source of clinically relevant biomarkers. In this context, the present study (that was conducted between October 2024 and September 2025 at the Haematology Department of the Merjan Teaching Hospital, Hillah, Iraq) aimed at evaluating the complement consumption patterns (specifically those of complement C3 and C4) and at determining their predictive value for haemolytic severity in AIHA by using a multimarker integration approach. A total of 40 Iraqi patients with AIHA were included in this study (55% females; mean age of 42.6 ± 14.3 years); these patients were categorized under mild

(30%), moderate (50%), or severe (20%) haemolysis according to their haemoglobin levels. Our findings exhibit a clear severity-associated pattern across the herein assessed haematological and biochemical parameters. More specifically, the haemoglobin levels declined progressively from 10.8 ± 0.9 g/dL in mild cases to 6.9 ± 0.7 g/dL in severe cases ($p < 0.001$), while the reticulocyte counts increased from $3.2\% \pm 0.9\%$ to $11.4\% \pm 2.1\%$, respectively. Similarly, the serum LDH levels rose from 320 ± 85 U/L to 910 ± 180 U/L, while the indirect bilirubin ones were found increased from 1.2 ± 0.4 mg/dL to 4.6 ± 1.1 mg/dL ($p < 0.001$). The herein undertaken complement profiling revealed reduced C4 levels in 65% of the patients and reduced C3 levels in 45% of them, with a combined depletion being observed in 37.5% of the cohort and in up to 75%–80% of the severe AIHA cases. Correlation analysis exhibited significant inverse relationships between complement levels and haemolytic markers (C3 *vs.* LDH levels: $r = -0.62$; C4 *vs.* LDH levels: $r = -0.68$; $p < 0.01$), alongside positive correlations with the haemoglobin levels (C3 levels: $r = 0.58$; C4 levels: $r = 0.63$). The identified strong positive correlation between C3 and C4 ($r = 0.72$, $p < 0.001$) – which was found increased to 0.81 in severe haemolysis cases – suggests a coordi-

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nated activation of the classical complement pathway. Moreover, multivariate logistic regression has identified the reticulocyte count as an independent predictor of severe haemolysis in AIHA (OR=1.88, 95% CI: 1.18–2.97, $p=0.006$), whereas the complement components displayed strong, yet non-independent associations. In the undertaken receiver operating characteristic analysis, a moderate diagnostic performance for individual markers (C3: AUC=0.74; C4: AUC=0.78) was identified, with the C4 levels showing higher sensitivity (82%) and the LDH ones showing higher specificity (85%). Notably, the combined multimarker model integrating C3, C4, and LDH levels is characterized by improved diagnostic accuracy (AUC=0.88), achieving balanced sensitivity (85%) and specificity (83%). Finally, the assessed multimarker scoring system has demonstrated a step-wise increase in the probability of severe haemolysis in AIHA, rising from less than 10% in the low-score categories to more than 75% in the high-score ones. In conclusion, the complement consumption patterns, particularly the combined depletion of C3 and C4, are closely associated with haemolytic severity in Iraqi AIHA patients; to this end, the integration of such parameters with conventional laboratory markers can significantly enhance diagnostic performance, provide a practical framework for risk stratification, and even guide clinical decision-making and therapy.

Keywords

autoimmune haemolytic anaemia; C3 complement; C4 complement; complement consumption; Iraq

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Conflicts of interest statement

None to declare.

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