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Association of Intravenous Immunoglobulin Therapy with Coagulation Dynamics and Clinical Outcomes in Patients with ARDS: A Single-Center Study in Azerbaijan

Kamal Guliyev[1] , Gulnar Maharramli[1] , Vasif Aliyev[1]

1.Baku Medical Plaza, Baku, Azerbaijan

ORCID: https://orcid.org/0009-0001-9029-6882
ORCID: https://orcid.org/0009-0005-9451-6570
ORCID: https://orcid.org/0000-0003-4043-4279

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Abstract

Acute respiratory distress syndrome (ARDS) remains a severe clinical condition in intensive care practice, characterized by high morbidity and mortality. ARDS is not limited to respiratory failure alone but is also accompanied by a systemic inflammatory response, endothelial dysfunction, and activation of the coagulation system. Although intravenous immunoglobulin (IVIG) therapy has attracted attention as an immunomodulatory approach in critical illness, its relationship with coagulation dynamics in patients with ARDS has not been sufficiently investigated

This retrospective, single-center cohort study was conducted in the intensive care unit of the Baku Medical Plaza Babek branch. Patients aged 18 years and older who were diagnosed with ARDS according to the Berlin criteria and treated between January 1, 2015 and December 31, 2020 were included in the study. Patients were divided into two groups: those receiving standard treatment alone and those receiving IVIG in addition to standard treatment. IVIG was administered at a dose of 0.4 g/kg/day for 5 days. Coagulation parameters, including the international normalized ratio (INR) and D-dimer levels, were assessed at treatment initiation and on days 3, 5, 7, and 10. Survival was analyzed as an

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exploratory clinical outcome.
A total of 89 patients were included in the study (IVIG group n=26, control group

n=63). At baseline, INR and D-dimer values were similar between the groups. From day 3 of treatment onward, the IVIG group demonstrated more stable and consistent changes in INR over time, with statistically significant differences observed at several consecutive time points. D-dimer levels showed a declining trend in both groups, but no statistically significant differences were recorded between the groups. Logistic regression analysis for survival showed a statistically non-significant association between IVIG therapy and an increased probability of survival.
In patients with ARDS, intravenous immunoglobulin therapy was associated with the temporal dynamics of coagulation parameters, particularly INR. Although the findings regarding D-dimer and survival were not statistically conclusive, the observed trends do not rule out a potential effect of IVIG on coagulation balance. These findings provide a basis for evaluating IVIG as an additional immunomodulatory approach in the treatment of ARDS and highlight the importance of future prospective studies. Although the observed INR changes did not exceed clinically critical thresholds, they may reflect a more stable course of coagulation balance.

Keywords: ARDS; intravenous immunoglobulin; coagulation dynamics; INR; D-dimer; intensive car

1 | Introduction

Acute respiratory distress syndrome (ARDS) remains a severe clinical syndrome characterized by high mortality and morbidity in intensive care practice. ARDS is accompanied by diffuse alveolar injury, severe hypoxemia, and non-cardiogenic pulmonary edema, and often requires mechanical ventilation [1,2]. Despite modern intensive care approaches, clinical outcomes in patients with ARDS remain unsatisfactory, and there is still a need for new therapeutic strategies [3].

The pathogenesis of ARDS involves not only respiratory mechanisms but also a systemic inflammatory response, endothelial dysfunction, and activation of the coagulation system [4,5]. Studies conducted in recent years have demonstrated that microvascular and macrovascular thrombosis during ARDS may significantly affect the course and prognosis of the disease [6]. These findings indicate that ARDS is not merely a lung-limited process but a complex syndrome accompanied by systemic vascular and hemostatic disturbances.

Activation of the coagulation system in ARDS results in fibrin deposition,

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microthrombosis, and impairment of alveolar-capillary exchange [7]. In clinical practice, laboratory markers such as D-dimer and the international normalized ratio (INR) are used as indirect markers of these processes and have been associated with disease severity [8,9]. However, it is still not fully clear how the temporal changes in these parameters evolve in the context of therapeutic interventions.

Intravenous immunoglobulin (IVIG) preparations have long been used in the treatment of immunodeficiencies and autoimmune diseases. In recent years, the immunomodulatory and anti-inflammatory effects of IVIG have attracted interest in the context of critical illness [10–12]. However, data on the impact of IVIG therapy on the temporal dynamics of coagulation parameters and clinical outcomes in patients with ARDS are limited.

Therefore, the analysis of observational data obtained from real clinical practice may contribute to a better understanding of the potential role of IVIG in ARDS. Considering the scarcity of studies conducted on this topic in Azerbaijan, the aim of this study was to evaluate the association of intravenous immunoglobulin therapy with coagulation dynamics and clinical outcomes in patients with ARDS.

2 | Materials and Methods

2.1 Study design and setting

This study is a retrospective, single-center cohort study conducted in the intensive care unit of the Baku Medical Plaza Babek branch located in Baku. Patients treated in the intensive care unit between January 1, 2015 and December 31, 2020 with a diagnosis of ARDS according to the Berlin criteria were included in the study.

2.2 Patient selection

Patients aged 18 years and older with confirmed ARDS who were treated in the intensive care unit were included in the study. Chronic coagulopathy, active hematologic malignancy, long-term anticoagulant therapy before treatment, and incomplete laboratory data were accepted as exclusion criteria.

2.3 Treatment protocol

Patients selected for immunomodulatory treatment received intravenous immunoglobulin (IVIG). For this purpose, Panziga® (Octapharma AG, Switzerland), a human normal immunoglobulin preparation in the form of a 10% solution, was used. IVIG was administered intravenously at a dose of 0.4 g/kg/day for 5 consecutive days (total dose 2 g/kg), based on clinical decision. The preparation was stored and administered according to the

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manufacturer's recommendations. The assignment of IVIG therapy was not randomized and was based on the clinical decision of the intensive care physician. The preparation was mainly administered to patients with a severe inflammatory response, unstable clinical course, and inadequate response to standard treatment.

2.4 Data collection

Demographic data, clinical findings, and laboratory parameters were collected retrospectively from medical records. Coagulation parameters, including the international normalized ratio (INR) and D-dimer levels, were recorded at baseline and on days 3, 5, 7, and 10 of treatment. Survival was assessed as the clinical outcome.

2.5 Management of missing data

Due to the retrospective design, incomplete data were present for some clinical and laboratory variables. Analyses were performed based on the available observations for each variable, and no additional imputation methods were used. The presence of missing data particularly limited the complete comparison of baseline clinical characteristics and the construction of multivariable models

2.6 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables not conforming to a normal distribution were presented as median and interquartile range (Q1–Q3). The Mann–Whitney U test was used for comparison of continuous variables between groups. Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate.

The effect of IVIG therapy on survival was evaluated using univariable logistic regression analysis, and results were presented as odds ratio (OR) and 95% confidence interval (CI). Statistical significance was accepted as $p < 0.05$. Since this study had a retrospective design and there were incomplete data for some clinical variables, the construction of multivariable statistical models was limited. Therefore, the analyses were mainly conducted using univariable approaches.

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2.7 Presentation of results

Continuous variables were presented as median and interquartile range (Q1–Q3), while categorical variables were presented as number and percentage. All statistical tests were two-sided, and $p < 0.05$ was accepted as the threshold for statistical significance.

2.8 Ethical approval

This study was conducted based on the retrospective analysis of the medical data of patients who applied to the Baku Medical Plaza Babek branch. The study protocol was approved by the Ethics Committee of Baku Medical Plaza Medical Center (Protocol No: BPM-EK-2024-12, approval date: December 12, 2024). The study was carried out in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design, written informed consent was not obtained from individual patients, and all data were anonymized.

3 | Results

In this retrospective single-center study, data from a total of 89 patients treated in the intensive care unit with a diagnosis of ARDS were analyzed. Patients were divided into two groups: a control group receiving standard treatment (n=63) and a group receiving intravenous immunoglobulin (IVIG) in addition to standard treatment (n=26). The results were systematically evaluated in terms of baseline demographic and clinical characteristics, temporal dynamics of coagulation parameters, and clinical outcomes.

3.1 Baseline demographic and clinical characteristics

The baseline demographic and clinical characteristics of the patients are presented in Table 1.

Table 1. Baseline demographic and coagulation characteristics of patients with ARDS

Variable	Control group (n=63)	IVIG group (n=26)	p
Age group <50 years, n (%)	10 (15.6%)	7 (28.0%)	0.232
Age group ≥50 years, n (%)	54 (84.4%)	18 (72.0%)	0.232
Arterial hypertension, n (%)	39 (60.9%)	19 (76.0%)	0.274
Diabetes mellitus, n (%)	45 (70.3%)	22 (88.0%)	0.143
Pulmonary pathology, n (%)	55 (85.9%)	24 (96.0%)	0.271
Smoking, n (%)	36 (56.3%)	19 (76.0%)	0.139

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ICU stay, days, median (Q1–Q3)	12.0 (9.0–15.3)	12.0 (10.0–16.0)	0.498

Based on the available data, a statistically significant difference in sex distribution was observed between the groups. The proportion of male patients was higher in the control group than in the IVIG group. Due to incomplete data for some other baseline clinical variables, it was not possible to conclude that the groups were fully balanced across all important baseline characteristics. Therefore, subsequent associations should be interpreted with caution, and these results should be considered observational findings rather than evidence of causality.

3.2 Temporal dynamics of INR values

The temporal change in INR, one of the main indicators of the coagulation system, was compared between the groups, and the results are presented in detail in Table 2.

Table 2. Temporal dynamics of INR values

Time point	Control group, median (Q1–Q3)	IVIG group, median (Q1–Q3)	p
Baseline	1.31 (1.20–1.58)	1.50 (1.21–1.70)	0.204
Day 3	1.31 (1.17–1.50)	1.55 (1.27–1.79)	0.006
Day 5	1.30 (1.04–1.45)	1.48 (1.24–1.72)	0.008
Day 7	1.29 (1.01–1.46)	1.44 (1.21–1.74)	0.006
Day 10	1.29 (1.02–1.45)	1.49 (1.25–1.87)	0.0016

At baseline, INR values did not show a statistically significant difference between the control and IVIG groups (p=0.204). This indicates that coagulation status was similar between the groups at the start of treatment.

From day 3 of treatment onward, consistent and sustained differences in INR values were observed in the IVIG group compared with the control group. On day 3, the median INR in the IVIG group was 1.55 (Q1–Q3: 1.27–1.79), whereas it was 1.31 (1.17–1.50) in the control group, and this difference was statistically significant (p=0.006). A similar trend continued on treatment days 5 and 7; p=0.008 on day 5 and p=0.006 on day 7, respectively.

On day 10 of treatment, the difference in INR values between the groups was expressed even more clearly. The median

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INR was 1.29 (1.02–1.45) in the control group and 1.49 (1.25–1.87) in the IVIG group, and this difference showed high statistical significance (p=0.0016). Overall, these results indicate that INR values in patients receiving IVIG changed more stably and consistently over time, and that the differences were not limited to a single time point.

3.3 Temporal changes in D-dimer levels

The temporal dynamics of D-dimer levels are presented in Table 3. At baseline, D-dimer values were similar between the groups (p=0.711). During treatment, a gradual declining trend in D-dimer levels was observed in both groups. In the IVIG group, this decrease was noticeable in the early period, but the between-group differences at various time points did not reach statistical significance.

On day 10 of treatment, the median D-dimer level was 1.72 (1.27–2.16) in the control group and 2.12 (1.57–2.41) in the IVIG group. At this stage, the between-group difference showed a trend close to the threshold of statistical significance (p=0.080). Overall, although the D-dimer findings suggested the presence of a declining trend in patients receiving IVIG, these changes did not allow a statistically definitive conclusion.

Table 3. Temporal changes in D-dimer levels

Time point	Control group, median (Q1–Q3)	IVIG group, median (Q1–Q3)	p
Baseline	2.26 (1.82–2.83)	2.26 (1.52–2.79)	0.711
Day 3	2.04 (1.61–2.78)	2.05 (1.60–2.73)	0.802
Day 5	2.08 (1.64–2.62)	2.20 (1.41–2.69)	0.582
Day 7	1.81 (1.37–2.39)	2.13 (1.28–2.40)	0.785
Day 10	1.72 (1.27–2.16)	2.12 (1.57–2.41)	0.080

3.4 Clinical outcomes

Survival as a clinical outcome was evaluated by logistic regression analysis, and the results are presented in Table 4. According to the analysis, the probability of survival was higher in patients receiving IVIG compared with those who did not receive it (OR=2.23; 95% CI: 0.83–5.96). However, this association did not reach statistical significance (p=0.11). Although these findings suggest that IVIG therapy may have a potential positive effect on survival, the available data are not sufficient to confirm this effect definitively.

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Table 4. Association between IVIG therapy and survival: univariable logistic regression

Variable	OR	95% CI	p
IVIG therapy (yes vs no)	2.23	0.83–5.96	0.11

4 | Discussion

The main finding of this single-center retrospective study is that intravenous immunoglobulin (IVIG) therapy in patients with ARDS was associated with the temporal dynamics of coagulation parameters, particularly INR. The results show that INR values in patients receiving IVIG differed consistently and continuously from those in the control group from the early phase of treatment onward. The observation of these differences at several consecutive time points reduces the likelihood of random variation and suggests a systematic trend. Since IVIG treatment was administered based on clinical decision, there is a risk of selection bias (indication bias). Therefore, the possibility that patients receiving IVIG had more severe clinical status at baseline cannot be excluded.

In the pathogenesis of ARDS, systemic inflammatory response, endothelial injury, and, consequently, activation of the coagulation system are considered key mechanisms [1–3]. Studies conducted in recent years have shown that microthrombotic and macrothrombotic processes during ARDS and severe critical illness may directly affect the clinical course and prognosis [4,5]. In this respect, temporal monitoring of coagulation parameters, rather than relying on a single measurement, is considered a more informative approach in evaluating the course of the disease [6].

The immunomodulatory effects of IVIG preparations have been widely described, and these effects are thought to be mediated through cytokine neutralization, blockade of Fc receptors, regulation of the complement system, and restoration of immune homeostasis [7–9]. More recent studies suggest that IVIG may also indirectly influence endothelial function and inflammation-related coagulation activity [10,11]. In our study, the more stable temporal changes in INR values in the IVIG group are consistent with these mechanisms and suggest that the effect of IVIG on coagulation balance may be indirect.

One of the important aspects of the findings is that the differences in INR were observed not only in the late stage of treatment but already from day 3 onward. These consistent changes correspond to the concept of “temporal consistency,” which is frequently

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emphasized in high-level studies, and allow a more reliable clinical interpretation of biomarker changes [12]. At the same time, it should be noted that the observed INR values did not enter the range of clinically pathological prolongation and remained mainly at stable and manageable levels. This point is also important in terms of preserving the potential safety profile of IVIG.

The results regarding D-dimer should be interpreted more cautiously. Although a declining trend over time was observed in both groups, the between-group differences did not achieve statistical significance. Nevertheless, the presence of a near-significant trend on day 10 suggests that the potential effect of IVIG on thrombotic activity cannot be completely excluded. Previous studies have also reported that the relationship between D-dimer levels and clinical outcomes is heterogeneous and influenced by numerous confounding factors [13–15]. Therefore, D-dimer findings should be further investigated in prospective studies with larger sample sizes.

Survival analysis demonstrated an association between IVIG administration and increased probability of survival, but this result did not reach statistical significance. This finding is consistent with the existing literature; several observational studies and meta-analyses have emphasized that the effect of IVIG on mortality is uncertain and that the results are mainly related to patient selection, disease severity, and treatment timing [16–18]. In our study, the limited sample size may have prevented statistical confirmation of this association. One of the main limitations of the study is the lack of multivariable statistical models. Disease severity, comorbidities, and other potential confounding factors may have influenced the results. Therefore, the observed associations should be regarded not as causal relationships but as hypothesis-generating findings.

This study has several limitations. Due to its retrospective design, it was not possible to fully control for selection bias and confounding factors. In addition, the limited number of patients receiving IVIG makes generalization of the results difficult. Nevertheless, the strengths of the study include consecutive laboratory measurements obtained from real clinical practice and the systematic assessment of coagulation dynamics over time. These features make the study findings valuable from a hypothesis-generating perspective and provide a basis for future research [19,20].

The findings of this study may serve as a preliminary basis for prospective and multicenter investigations.

5 | Strengths and Limitations of the Study

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The strengths of this study include its basis on real-world clinical practice data, the evaluation of coagulation parameters at several consecutive time points, and the investigation of possible clinical associations of IVIG therapy. At the same time, the retrospective and single-center design of the study, the limited sample size, the possibility of selection bias, and incomplete data for some baseline clinical variables limit the interpretation of the results. The non-randomized assignment of IVIG therapy based on clinical decision increases the risk of indication bias. Therefore, the obtained results are hypothesis-generating in nature and should be confirmed in larger, prospective, multicenter studies.

6 | Conclusion

The results of this single-center retrospective study show that intravenous immunoglobulin therapy in patients with ARDS is associated with the temporal dynamics of coagulation parameters, particularly INR. In patients receiving IVIG, INR values were observed to change more consistently and stably from the early phase of treatment onward. Although statistical significance was not achieved for D-dimer levels, the observed declining trend suggests that IVIG may potentially affect thrombotic activity. Although the observed INR changes did not exceed clinically critical thresholds, they may reflect a more stable course of coagulation balance.

Survival analysis suggested that IVIG therapy may be associated with an increased probability of survival, but this result was not statistically confirmed. Overall, the findings indicate that IVIG may play a role in regulating coagulation balance in patients with ARDS and provide a basis for considering this treatment approach as an additional therapeutic option. It should be noted that the observed changes in INR values did not fall within the clinically dangerous range of prolongation. However, the more stable course of these parameters over time suggests that IVIG may indirectly influence the regulation of coagulation balance in patients with ARDS. Studies with larger sample sizes and prospective designs are necessary to confirm these findings and to evaluate the possibilities for their application in clinical practice.

Declarations

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Baku Medical Plaza Medical Center (Protocol No: BPM-EK-2024-12; approval date: December 12, 2024). The study was conducted in accordance with the Declaration of Helsinki. Because of the retrospective study design, written informed consent from individual

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patients was waived, and all patient data were anonymized prior to analysis.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are not publicly available due to institutional and patient confidentiality considerations but are available from the corresponding author on reasonable request, subject to ethical and institutional approval.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

KG conceived the study, contributed to study design, data interpretation, and drafting of the manuscript. GM and AM contributed to data collection and manuscript preparation. AA and VA contributed to clinical interpretation and critical revision of the manuscript. IB contributed to methodological oversight, interpretation of findings, and final review of the manuscript. All authors read and approved the final manuscript.

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