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Research Article

Actemra Therapy and Survival Outcomes in Critically Ill COVID-19 Patients: A Retrospective Analysis

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ABSTRACT

Tocilizumab (Actemra), an interleukin-6 receptor antagonist, has demonstrated potential as a therapeutic option for severe COVID-19 by mitigating the hyperinflammatory response associated with disease progression. This study aimed to assess the impact of Actemra therapy on survival outcomes among hospitalized patients with severe or critical COVID-19 in a real-world setting. A retrospective observational cohort study was conducted at a COVID-19 isolation center in Al-Marj City, Libya. Adult patients with severe or critical COVID-19 admitted between August 2020 and December 2021 were included. Data on demographics, clinical status, and laboratory results were extracted from medical records. The primary outcome was survival status, with secondary outcomes being hospital stay length and hospitalization-free survival time. A total of 195 patients were included (median age 58 years; 71.3% male), of whom 26.2% received Actemra. The Actemra group had higher ICU admission rates, gastrointestinal symptoms, and CPAP use, but reduced the prevalence of diabetes and hypertension. Actemra recipients experienced longer hospital stays and higher levels of inflammatory markers. Kaplan–Meier analysis revealed significantly longer survival in the Actemra group (mean 29.9 vs. 10.1 days, $p < 0.001$). Cox regression indicated a 77% reduction in hospitalization risk with Actemra (HR 0.230, $p < 0.001$). Logistic regression showed over fourfold increased survival odds (OR 4.552, $p = 0.001$). The study concluded that Actemra therapy significantly improved survival and reduced hospitalization risk in severe and critical COVID-19 patients. These findings support its targeted use in hyper inflammatory patients, with further randomized trials needed to confirm benefits and safety.

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1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease 2019 (COVID-19), which has emerged as one of the most pressing global health issues of the 21st century. Because it was the first time it was identified
The pandemic has placed a significant burden on healthcare systems around the world, resulting in widespread sickness and mortality in late 2019. Severe COVID-19 infections are frequently linked to high death rates, multi-organ failure, and acute respiratory distress syndrome, particularly in those who are hospitalized or critically ill patients [1, 2].
A characteristic feature of severe COVID-19 is the emergence of a hyperinflammatory condition, commonly referred to as a cytokine storm. This condition is characterized by marked increase levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), and is associated with rapid clinical deterioration [3, 4]. Elevated IL-6 levels are strongly correlated with disease severity, increased oxygen requirements, prolonged hospital stays, and higher mortality rates [5]. Consequently, targeting IL-6 inhibition has emerged as a promising therapeutic strategy to reduce the inflammation and improve clinical outcomes in patients with severe COVID-19 [6].
Tocilizumab (Actemra), a humanised recombinant monoclonal antibody that inhibits both soluble and membrane-bound IL-6 receptors, blocks IL-6–mediated signalling and has been widely used in treating autoimmune and inflammatory diseases [6]. The potential benefits of Tocilizumab in COVID-19 include reducing inflammation, preventing progression to respiratory failure, and enhancing survival. Numerous randomized controlled trials (RCTs) and meta-analyses have investigated this potential benefit, yielding mixed results. The RECOVERY trial found that adding Tocilizumab when added to standard care significantly reduced mortality in hospitalized, hypoxic COVID-19 patients with elevated inflammatory markers [7]. Similarly, the REMAP-CAP trial reported improved survival and reduced progression to organ support in critically ill patients [8]. However, other studies, such as the COVACTA trial, did not find significant differences in mortality or clinical status at day 28 [9], while smaller RCTs and observational studies reported varied outcomes [10, 11]. This variability is reflected in systematic reviews; some meta-analyses report a significant reduction in mortality and increased hospital discharge rates [12, 13], while others note that analyses limited to peer-reviewed RCTs sometimes fail to find a significant association [13]. Additionally, the drug's safety profile, particularly concerning the increased risk of secondary infections, remains a topic of discussion [12]. A significant gap persists in real-world evidence from low- and middle-income countries (LMICs), as the current body of research on this intervention is predominantly derived from high-resource settings where healthcare infrastructure and patient populations may not be comparable. The present study was undertaken to assess the impact of Actemra therapy on survival outcomes within a real-world hospital context. Even in a low-resource environment, we predicted that Actemra treatment would be linked to better survival among severely sick COVID-19 patients.

2. Methodology

2.1.Study Design and Location

A retrospective observational study was carried out at the COVID-19 Isolation Center in Al-Marj City, Libya.

2.2.Study Population

The study included adult patients aged 18 years and older who were admitted to the isolation center between August 2020 and December 2021 with a clinical classification of severe or critical COVID-19. Confirmation of SARS-CoV-2 infection was confirmed by positive real-time reverse transcription polymerase chain reaction (RT-PCR) test performed on nasopharyngeal swab samples, or by a validated rapid antigen test.

The inclusion criteria required that patients be admitted to the isolation center during the

study period, have laboratory confirmed SARS-CoV-2 infection, and meet the definition of severe or critical COVID-19 based on clinical and radiological assessments.

The exclusion criteria included patients with incomplete medical records and those who were moved to another hospital before their clinical outcomes were assessed.

2.3.Data Collection

The data were collected from the hospital's electronic and paper medical records using a standardized data collection form. The variables collected included demographic information such as age, sex, and vaccination status; comorbidities such as diabetes, hypertension, cardiovascular disease, chronic kidney disease, respiratory disease, and cerebrovascular accident; clinical characteristics including ICU admission, CPAP use, and respiratory or gastrointestinal symptoms; and laboratory findings such as complete blood count, renal and liver function tests, inflammatory markers (CRP, ferritin, D-dimer, lactate dehydrogenase, and procalcitonin), cardiac markers (troponin and CK-MB), and blood gas parameters. Treatment-related data included the receipt of Actemra and other supportive or pharmacological therapies. Outcomes assessed were survival status (alive or deceased), length of hospital stay, and hospitalization-free survival time. Due to the fact that the study was retrospective and used anonymized data, the need for patient consent was waived. All data were handled in accordance with the Declaration of Helsinki and the national data protection regulations.

2.4. Statistical analyses

IBM SPSS Statistics (version 22; IBM Corp., Armonk, NY, USA) was used to analysed the data. Differences between categorical variables were assessed using the chi-square or Fisher's exact test, depending on the data distribution. (Actemra vs. non-Actemra). Continuous variables which were reported as medians and interquartile ranges (IQRs) were compared using the Mann–Whitney U test. For survival analysis, time-zero was defined as the date of hospital admission. The primary outcome was time to death, with patients discharged alive censored on their date of discharge. The Kaplan-Meier method was used to estimate survival distributions, which were then compared using the log-rank test. A Cox proportional hazards regression model was used to estimate adjusted hazard ratios (HRs) for mortality. Covariates for adjustment (e.g., age, key comorbidities, and disease severity) were pre-selected based on their clinical significance and proven association with COVID-19 outcomes in the literature. Multivariable logistic regression was used to identify independent predictors of survival. Acknowledging the inherent limitations of an observational study, confounding by indication is a major consideration, as the decision to administer Actemra was made by treating clinicians based on disease severity and clinical judgment, rather than randomization. All statistical tests were two-tailed, and a p-value was considered statistically significant if it was less than 0.05.

3. Results

Among the 195 patients included in the study, the majority were male (71.3%) and unvaccinated (92.3%). A high proportion required ICU admission (69.7%). The most prevalent comorbidities were diabetes (56.4%) and hypertension (53.3%). Clinically, dyspnea (99.5%), cough (89.7%), and fever (87.2%) were the most frequent symptoms. Actemra was administered to 51 patients (26.2%).

3.1 Actemra vs. Non-Actemra

Chi-square tests showed that Actemra recipients had higher ICU admission rates (92.2% vs. 61.8%, $p < 0.001$), gastrointestinal symptoms (60.8% vs. 40.3%, $p = 0.012$), and CPAP use (92.2% vs. 61.8%, $p < 0.001$) than non-recipients. They had lower rates of diabetes (43.1% vs. 61.1%, $p = 0.026$) and hypertension (41.2% vs. 57.6%, $p = 0.043$), and all were PCR-positive for COVID-19 ($p = 0.001$).

Mann–Whitney U tests indicated the Actemra group was younger (mean rank 75.0 vs. 106.2, p = 0.001) but had longer hospital stays (133.5 vs. 84.7, p < 0.001). They had higher platelet counts (p < 0.001), bilirubin (p = 0.04), LDH (p < 0.001), D-dimer (p = 0.02), ferritin (p = 0.01), and random blood sugar (p = 0.002), but lower urea (p = 0.03), creatinine (p = 0.03), and procalcitonin (p < 0.001). These differences highlight the presence of confounding by indication, where the treatment was allocated based on perceived severity.

3.2.Survival Analysis

Among the 195 patients included in this study, 111 (56.9%) died and 84 (43.1%) survived. The association between Actemra therapy and survival status was examined using the chi-square test (Table 1). The results showed a statistically significant relationship between Actemra use and survival outcomes *(p < 0.001)*, indicating that patients who received Actemra had a higher survival rate than those who did not.

Table1: Association between Actemra Therapy and Survival Outcomes

Survival Status	Actemra Group (51)	Non-Actemra Group (144) _	Total (195)
Survived, n (%)	35 (68.6%)	49 (34.0%)	84 (43.1%)
Died, n (%)	16 (31.4%)	95 (66.0%)	111 (56.9%)

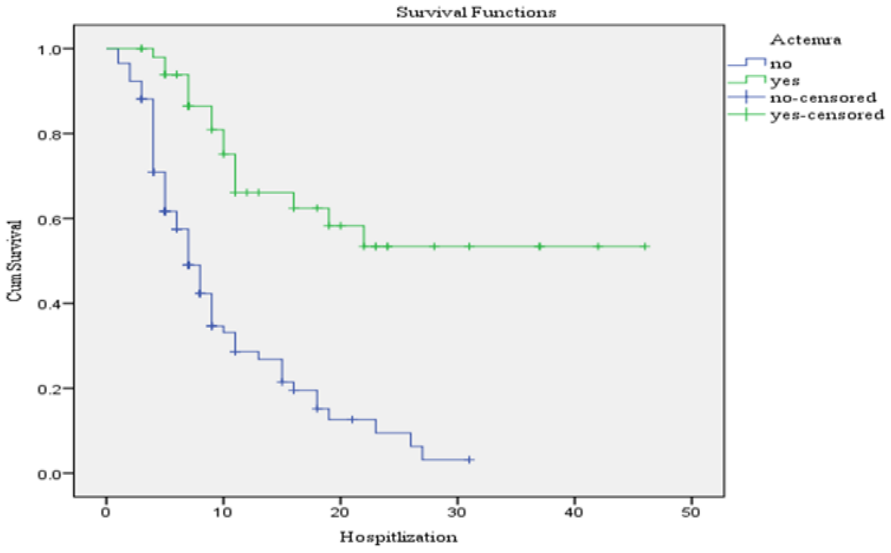

Figure 1: Kaplan–Meier Survival Curves for Actemra and Non-Actemra Groups.

Table 2: Mean Survival Time by Actemra Treatment Group

Actemra Treatment	Mean Survival Time (days)	95% CI Lower	95% CI Upper
No	10.1	8.48	11.73
Yes	29.9	23.86	35.92

3.2.1.Kaplan–Meier Survival Analysis

Kaplan–Meier survival curves demonstrated a significantly longer survival time in patients who received Actemra than in those who did not (Figure 1) The survival probability remained higher in the Actemra group across the study period, with the log-rank test confirming a statistically significant difference ($p < 0.001$). The mean survival time for the Actemra group was 29.9 days (95% CI: 23.86–35.92), whereas it was 10.1 days (95% CI: 8.48–11.73) for the non-Actemra group (Table 2). The log-rank test indicated a highly significant difference between the two groups (χ^2 (1) = 33.08, $p < 0.001$) (Table 3). These results indicated a significant survival rate benefit associated with Actemra treatment during the study period.

3.2.2.Cox Proportional Hazards Regression

Predictors of hospitalization risk were identified using a multivariable Cox proportional hazards regression model after adjusting for potential confounders. (Table 3). Actemra treatment demonstrated a strong independent association with reduced hospitalization risk, exhibiting a hazard ratio (HR) of 0.230 (95% CI: 0.128–0.412, $p < 0.001$), This corresponds to a 77% decrease in the hazard of hospitalization among recipients compared to non-recipients. Increasing age was also a significant predictor, with each additional year associated with a 2.2% rise in hospitalization risk (HR: 1.022, 95% CI: 1.007–1.036, $p = 0.003$). Diabetes mellitus showed a trend toward increased risk (HR = 1.471, 95% CI: 0.962–2.248), though this association was not statistically significant ($p = 0.075$). Other variables, including hypertension, white blood cell count, and troponin levels, did not reach significance in the adjusted model (all $p > 0.05$). These findings indicate that, after adjustment for confounders, Actemra use and older age are key determinants of hospitalization risk, while the other clinical variables examined did not contribute substantially to the model.

Table 3: Multivariable Cox Regression Analysis of Predictors for Hospitalization

Variable	B (SE)	Hazard Ratio (HR)	95% CI for HR	*p*-value
Actemra (yes vs. no)	−1.470 (0.298)	0.230	0.128–0.412	<0.001
Age (per year)	0.022 (0.007)	1.022	1.007–1.036	0.003
Diabetes (yes vs. no)	0.386 (0.216)	1.471	0.962–2.248	0.075
Hypertension (yes vs. no)	−0.125 (0.209)	0.882	0.586–1.329	0.548
WBC count	−0.002 (0.009)	0.998	0.980–1.016	0.837
Troponin	0.421 (0.268)	1.524	0.901–2.576	0.116

3.2.3.Logistic Regression Analysis

Predictors of survival (alive vs. deceased) were assessed by using a multivariable logistic regression model after adjusting for potential confounders, including age, diabetes mellitus (DM), CKMB, troponin, D-dimer, procalcitonin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin (Table 4). Actemra therapy was a strong independent predictor of survival, with an odds ratio (OR) of 4.552 (95% CI not shown, $p = 0.001$), demonstrating that, after adjusting for other factors, patients treated with Actemra had a survival rate that was more than four times higher than those who did not

receive the medication. Increasing age was significantly linked to lower odds of survival (OR = 0.968, p = 0.007), indicating that the odds of survival decreased by around 3.2% for each additional year of age. Higher D-dimer levels were also significantly associated with increased mortality (OR = 1.000, p = 0.031), suggesting that elevated coagulation activity may be associated with poorer outcomes. Other variables, including diabetes mellitus and inflammatory markers (CRP, ESR, and ferritin), showed no statistically significant associations ($p > 0.05$) with survival in the adjusted model.

Table 4. Multivariable Logistic Regression Analysis of Predictors for Survival

Variable	B	S.E.	Wald	df	Sig.	Exp(B)
Actemra	1.516	0.453	11.208	1	0.001	4.552
Age	-0.033	0.012	7.161	1	0.007	0.968
DM	-0.276	0.349	0.626	1	0.429	0.759
CK-MB	-0.006	0.005	1.133	1	0.287	0.994
Troponin	-0.645	0.512	1.586	1	0.208	0.525
D-dimer	0.000	0.000	4.633	1	0.031	1.000
Procalcitonin	-0.415	0.214	3.761	1	0.052	0.660
CRP	-0.001	0.002	0.461	1	0.497	0.999
ESR	-0.005	0.006	0.634	1	0.426	0.995
Ferritin	0.000	0.000	0.481	1	0.488	1.000
Constant	3.561	1.014	12.330	1	0.000	35.187

4. Discussion

Actemra treatment was substantially linked to better survival in this cohort analysis of 195 hospitalized patients, results in contrast to standard care. It is important to note that the substantial effect size observed may be influenced by the observational design and confounding factors and does not prove causation. Our findings of a significant association with reduced mortality align with results from large-scale trials, such as the RECOVERY trial [7], and meta-analyses that have confirmed the efficacy of IL-6 receptor antagonists in reducing short-term mortality (summary OR ~0.86) and the progression to mechanical ventilation [17]. A meta-analysis of individual patient data revealed that IL-6 suppression also improved discharge rates and reduced the probability of death (HR ~0.75–0.85) [17]. However, our study's level of relationship (OR = 4.552) was significantly more than the summary estimates from meta-analyses of randomized trials (e.g., RR ~0.89) [18], this discrepancy likely reflects key differences in study design, patient selection, and unmeasured confounding inherent to our real-world analysis, rather than a superior treatment effect. The observed benefit is consistent with some retrospective cohort studies [19].

However, the COVACTA trial yielded neutral results, showing no significant benefit in mortality or clinical status at day 28 [9], and other randomized trials have reported mixed outcomes [10, 11]. This inconsistency in the literature is a recognized challenge, often attributed to high heterogeneity (I^2 up to 88% in some meta-analyses [20]) arising from variations in patient selection, timing of treatment, and concomitant therapies [14, 8]. Observational studies have suggested that earlier initiation, particularly in patients with elevated IL-6 or CRP levels, yields greater benefits [20]. This is supported by evidence indicating that Actemra is most effective in critically ill patients with severe inflammatory responses, potentially explaining the positive results in our cohort, which exhibited high

baseline inflammatory markers [21, 16]. In our study, the higher baseline LDH and ferritin levels in the Actemra group may reflect a more severe inflammatory phenotype, supporting targeted IL-6 blockade in such cases. Lower procalcitonin levels suggest fewer bacterial co-infections, potentially contributing to better outcomes and aligning with findings that lower procalcitonin levels are predictors of a positive response [22].

The findings support the early and targeted administration of Actemra in patients exhibiting severe disease and signs of hyperinflammation, aligning with its proposed mechanism of action in mitigating cytokine release syndrome [20]. The integration of biomarker-based selection, such as LDH, ferritin, and procalcitonin, may enhance treatment efficacy. As demonstrated in the RECOVERY and REMAP-CAP trials, the concurrent use of corticosteroid therapy may augment efficacy [7, 8], underscoring the value of combination therapeutic approaches. Typical dosing regimens of 8 mg/kg (maximum 800 mg) intravenously, occasionally repeated, were effectively employed in this and other studies [21, 23]. However, the potential for an increased risk of secondary infections associated with Actemra use warrants consideration [16]. Although our study did not primarily focus on adverse events, existing literature presents mixed findings regarding this risk [18, 24]. Consequently, vigilant monitoring for bacterial or fungal infections remains a critical precaution for patients receiving IL-6 blockade, particularly those with pre-existing immunocompromised conditions.

The strengths of our study lie in the robust sample size (n = 195), which enhances its statistical power. We employed a variety of statistical methods, including survival analysis and multivariable regression. Furthermore, the use of real-world data increases the generalizability of our findings to clinical practice.

The retrospective and observational nature of the study restricts the ability to establish causal relationships. The presence of baseline differences between groups raises the possibility of residual confounding, and the lack of randomization, along with unmeasured covariates, may have influenced the results. Laboratory data only reflect baseline values, without accounting for post-treatment trends. As with many real-world studies, the timing of treatment administration was not standardized, which is a critical factor that could have influenced outcomes. Additionally, data on secondary infections, a key safety endpoint highlighted in the literature, were not systematically captured.

5. Conclusions

The study concluded that Actemra therapy was associated with a significantly higher chance of survival and reduced hospitalization risk in this cohort of patients. These results align with the growing evidence supporting IL-6 blockade in severe inflammatory diseases, particularly COVID-19; however, further prospective randomized controlled trials should be conducted to confirm survival benefits, along with subgroup analyses to refine patient selection and research on the optimal timing of Actemra administration. Long-term follow-up studies, as well as research on secondary infections and adverse events in specific patient populations, are also necessary.

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Conflicts of Interest

The authors declare that they have no conflicts of interest

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