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Recovery trajectories of TAFRO syndrome: a single-center case series highlighting prolonged thrombocytopenia and anasarca

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ABSTRACT

TAFRO syndrome is a rare systemic inflammatory disorder characterized by thrombocytopenia, anasarca, fever or inflammation, reticulin fibrosis or renal dysfunction, and organomegaly. Despite increasing recognition, its natural history, particularly the timeline of organ-specific recovery, remains poorly understood. We retrospectively analyzed seven patients, encompassing nine treatment courses, diagnosed with TAFRO syndrome at our institution. Time to recovery was assessed across four clinical domains—renal dysfunction, systemic inflammation, anasarca, and thrombocytopenia—using predefined objective criteria. The median time to recovery was 7.0 days for renal dysfunction, 21.0 days for systemic inflammation, 24.0 days for anasarca, and 46.0 days for thrombocytopenia. Recovery of thrombocytopenia and anasarca tended to be delayed compared with that of renal dysfunction and systemic inflammation, with thrombocytopenia showing the longest median time to recovery. These findings indicate substantial heterogeneity in organ-specific recovery trajectories in TAFRO syndrome, with hematologic and fluid-related manifestations resolving more slowly than inflammatory or renal abnormalities. Recognition of domain-specific recovery timelines may aid interpretation of treatment responses and support more balanced, individualized management strategies.

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anasarca

1. Introduction

TAFRO syndrome is a rare systemic inflammatory disorder characterized by thrombocytopenia, anasarca, fever/inflammation, reticulin fibrosis and/or renal insufficiency, and organomegaly. First reported by Takai et al. in 2010, the syndrome presents with an acute clinical course and a unique constellation of symptoms not attributable to other diseases [1]. Since its initial description, TAFRO syndrome has been recognized internationally and is now often considered part of the spectrum of idiopathic multicentric Castleman disease (iMCD), particularly as a hyperinflammatory subtype termed iMCD-TAFRO.

This growing recognition of TAFRO syndrome, however, is accompanied by variations in diagnostic frameworks across regions. The international consensus definition proposed by Fajgenbaum and Nishimura et al. requires lymph node histopathology consistent with iMCD, whereas the Japanese criteria proposed by Masaki et al. emphasize clinical findings and allow diagnosis without lymph node biopsy, facilitating recognition in patients with severe or rapidly progressive disease [2–4].

Although TAFRO syndrome shares some pathogenic features with iMCD, including elevation of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), its clinical course is often more fulminant, and the treatment response is more variable. Despite the increasing recognition of this syndrome, its disease trajectory remains poorly characterized. Most existing literature consists of individual case reports or small series with limited data on longitudinal clinical outcomes. In particular, the timeline of recovery across different organ systems, such as renal function, systemic

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inflammation, anasarca, and thrombocytopenia, has not been systematically studied. This information is critical for optimizing therapeutic strategies, evaluating treatment responses, and supporting appropriate decisions regarding intensification or tapering of therapy.

In this retrospective case series, we investigated the temporal patterns of organ-specific recovery in patients diagnosed with TAFRO syndrome. By analyzing the recovery time of key clinical domains, we aimed to better understand the natural history of the disease and identify practical considerations for its management and follow up. Clarifying these temporal dynamics may contribute to establishing individualized treatment plans and optimizing supportive care for TAFRO syndrome.

2. Patients and methods

2.1. Study design

This retrospective case series analyzed the clinical course of patients diagnosed with TAFRO syndrome at our institution between January 2009 and October 2024. All patients fulfilled the diagnostic criteria for TAFRO syndrome as defined by Masaki et al. in 2015 [5].

For the analysis of the clinical course, day 1 was defined as the day treatment was initiated. The number of days required for recovery in each domain, renal function, systemic inflammation, anasarca, and thrombocytopenia, was recorded. Recovery in each domain was defined as follows:

- Recovery of renal function was defined as the first day on which serum creatinine showed a sustained downward trend from the peak value, defined as a decrease observed in at least two consecutive measurements without subsequent rebound that could not be attributed to renal replacement therapy.
- Recovery of systemic inflammation was defined as the day on which the C-reactive protein (CRP) level returned to the normal range.
- Recovery of anasarca was defined as the day body weight and/or abdominal circumference began to show a sustained decrease that could not be attributed to drainage procedures.
- Recovery from thrombocytopenia was defined as the day when the platelet count reached $\geq 50 \times 10^3/\mu\text{L}$ on a sustained basis without platelet transfusion.

This study protocol was approved by our institutional ethics review board (B250052) and was conducted in accordance with the principles of the Declaration of Helsinki. Because this was a retrospective study, we disclosed the study information at our hospital. Obtaining patient consent was not required according to the committee's procedures.

2.2. Data collection

Clinical and pathological data were retrospectively collected from the patients' medical records. These included baseline patient demographics (sex, age at treatment initiation, comorbidities, initial symptoms, and duration from symptom onset to initiation of treatment), blood test results (platelet count, alkaline phosphatase (ALP), creatinine, CRP, immunoglobulin G (IgG), IL-6, VEGF, and soluble IL-2 receptor), biopsy results (bone marrow and lymph node), treatment details, and clinical outcomes. In Japan, serum ALP levels were measured using the JSCC method until March 2020, after which the IFCC method was adopted. Because our study period spanned both methods, all JSCC values were converted into IFCC-equivalent values using a standard conversion factor ($\text{JSCC} \times 0.35 \approx \text{IFCC}$), and analyses were performed based on IFCC values.

2.3. Statistical analysis

Graphs were generated using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). The Wilcoxon signed-rank test was used to compare the time from treatment initiation to the recovery of each organ dysfunction, followed by post hoc analyses where appropriate. The Bonferroni correction

was applied for multiple comparisons, and a p -value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Seven patients were included in the study. Two of these patients experienced relapse after remission; therefore, nine treatment courses were reviewed and analyzed. The baseline characteristics of the patients are summarized in [Table 1](#). All patients were of Japanese origin. The median age at treatment initiation was 56.9 years (range: 17–71 years), with four males and three females in the cohort.

Fever was the initial symptom in all cases except for case 4. Other frequently observed presenting symptoms included gastrointestinal manifestations, such as abdominal pain, nausea, and vomiting, as well as signs of anasarca, including generalized edema and weight gain. The duration from symptom onset to initiation of treatment ranged from 19 to 79 days (median 54 days), indicating variability in the timing of diagnosis and treatment initiation.

All patients demonstrated abnormal levels of inflammatory and disease-related biomarkers at baseline ([Table 1](#)). The maximum serum CRP level had a median of 15.34 mg/dL with an interquartile range (IQR) of 5.335–21.495 mg/dL, indicating marked systemic inflammation in all cases. Maximum serum creatinine levels showed a median of 1.85 mg/dL (IQR: 1.195–3.025 mg/dL), reflecting renal dysfunction of varying severity. Maximum alkaline phosphatase (ALP) levels were also elevated, with a median of 249 U/L (IQR: 198.65–285.1 U/L), exceeding the normal reference range (38–113 U/L). Maximum IgG concentrations varied among patients, with a median of 1650 mg/dL (IQR: 1036–2364 mg/dL); mildly elevated IgG levels were observed in Cases 2, 4, and 6. Regarding autoantibody profiles, anti-SS-A antibodies were positive in Cases 1 and 2, anti-SS-B antibodies were positive in Case 2, and a direct Coombs test was positive in Case 6. However, none of the patients fulfilled the classification criteria for systemic autoimmune diseases based on the available clinical, serological, and histopathological data. In contrast, the minimum platelet count (PLT) observed during the disease course had a median of $14 \times 10^3/\mu\text{L}$ (IQR: $9.5\text{--}24.0 \times 10^3/\mu\text{L}$), confirming the presence of thrombocytopenia in all patients.

Serum IL-6 and VEGF levels were measured prior to treatment in six treatment courses (Cases 2, 3, 4, 6-1, 6-2, and 7). All six cases exhibited elevated IL-6 levels above the normal reference range; however, the magnitude of elevation varied substantially among patients. In contrast, VEGF levels showed greater heterogeneity; four cases (Cases 3, 6-1, 6-2, and 7) demonstrated marked elevation, whereas two cases (Cases 2 and 4) had VEGF concentrations within the normal range. Notably, no clear correlation was observed between IL-6 and VEGF levels (Spearman's rank correlation, $\rho = -0.60$, $p = 0.242$; [Supplementary Figure S1](#)), suggesting that the activation of these pathways may vary among patients with TAFRO syndrome.

All patients fulfilled the diagnostic criteria for TAFRO syndrome proposed by Masaki et al. All patients, except for the patient in Case 4, underwent lymph node biopsy, which revealed pathological features consistent with idiopathic multicentric Castleman disease (iMCD). Based on the international consensus criteria proposed by Nishimura et al. all cases were classified as iMCD-TAFRO, except for Case 4, which was categorized as TAFRO syndrome without histopathological confirmation of iMCD ([Table 1](#)). In Case 2, a prior episode of isolated thrombocytopenia that resolved after *Helicobacter pylori* eradication without immunosuppression was excluded from the TAFRO disease course, and the diagnosis was supported by lymph node biopsy findings.

All nine treatment courses included glucocorticoids (GCs) as the initial therapy. In addition, various immunosuppressants and biologics were administered, including tocilizumab, calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolate mofetil (MMF), and rituximab. Thrombopoietin receptor agonists (TPO-RAs) were used temporarily in three treatment courses (Cases 1–2, 4, and 7), particularly in cases of refractory thrombocytopenia.

Renal replacement therapy was required in Cases 1–2 and 3, and plasma exchange was performed in Cases 1–2 and 4 as supportive therapy. Notably, all of these interventions were initiated during

Table 1. Baseline characteristics and manifestation of the patients.

Case	1-1	1-2	2	3	4	5	6-1	6-2	7
Sex	male	male	female	male	male	female	female	female	male
Age	61	70	68	17	71	52	61	62	50
symptoms	fever, headache, abdominal pain	fever, abdominal pain	fever, edema, purpura	fever, vomiting, chest pain, abdominal pain	abdominal bloating, edema	fever, fatigue, weight gain	fever, edema, vomiting, diarrhea	fever, diarrhea, loss of appetite	fever, edema, hematuria
The duration to treatment (days)	79	19	74	70	24	71	44	54	30
Blood test results									
CRP(max), mg/dL	15.34	24.44	2.70	21.88	21.11	19.82	5.85	5.21	5.46
PLT(min), 10 ³ /μL	11	18	22	68	26	11	14	2.6	8
Cr(max), mg/dL	6.70	2.32	1.61	2.63	1.85	1.31	1.08	1.08	3.42
ALP(max), U/L (38–113)	265.0	217.3	252.4	305.2	235.2	249	415	110	180
IgG(max), mg/dL (861–1747)	1650	1262	2698	810	2018	698	2896	2030	1284
Rheumatoid factor	–	+	–	N/A	–	–	–	–	–
Anti-nuclear antibody (pattern, titer)	Sp 640	Sp 160	Sp 160	–	Sp 40	Sp 80	Sp 160 Ho 40	Sp 160 Ho 160	Sp 40 Ho 40
Anti-dsDNA antibody	–	–	–	N/A	–	–	–	–	–
Anti-RNP/Sm antibody	–	–	–	N/A	–	–	–	–	–
Anti-SS-A antibody	N/A	+	+	N/A	–	–	–	N/A	–
Anti-SS-B antibody	N/A	–	+	N/A	N/A	–	N/A	N/A	–
Anti-phospholipid antibodies	–	–	+	N/A	–	–	N/A	N/A	+
PA-IgG	–	+	–	–	–	–	Direct Coombs	–	–
Other autoantibodies	–	–	–	–	–	–	18.1	13.5	11.9
IL-6, pg/mL (≤7.0)	45.3	N/A	24.2	70.0	26.3	2.8	–	–	–
VEGF, pg/mL (143.1–658.8)	N/A	N/A	394	729	86.8	N/A	15792.9	6597.0	4775.2
Biopsy findings									
Bone marrow	+	+	+	+	+	+	+	+	+
Megakaryocytosis	+	+	+	+	+	+	+	+	+
reticulon fibrosis	+	+	+	+	+	+	+	+	+
Lymph node	Mix	N/A	HV	Mix	N/A	Mix	Mix	Mix	Mix
Classification	IMCD-TAFRO	IMCD-TAFRO	IMCD-TAFRO	IMCD-TAFRO	TAFRO w/o IMCD	IMCD-TAFRO	IMCD-TAFRO	IMCD-TAFRO	IMCD-TAFRO
Treatment	GC ISS CHOP →TCZ	TOF+TAC →MMF	TCZ →TAC	TAC	TAC →TOF	CyA →TAC →MMF	CyA	RTX	MMF+TAC →RTX
Renal replacement therapy	–	+	–	–	+	–	–	–	+
Plasma exchange	–	+	–	+	–	–	–	–	–
Pleural drainage	+	+	+	–	+	–	–	–	–
Peritoneal drainage	+	+	+	–	+	–	–	–	–
Infectious complications	+	+	+	–	+	–	–	–	–
Length of hospital stay at our institution (days)	101	127	144	79	63	54	57	50	82

CHOP: CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone), Cr: creatinine, CRP: C-reactive protein, CyA: cyclosporine, GC: glucocorticoid, Ho: homogenous, HV: hypervascular type, IgG: immunoglobulin G, IL-6: interleukin-6, VEGF: vascular endothelial growth factor, Mix: hypervascular and plasma cell type, MMF: mycophenolate sodium, N/A: not available, PLT: platelet, Sp: speckled, TAC: tacrolimus, TCZ: tocilizumab, TOF: tofacitinib, TPO-RAS: thrombopoietin receptor agonists. ALP values are presented as IFCC-equivalent values. JSCC values were converted to IFCC units using a standard factor.

Table 2. Time to recovery for each clinical domain (days).

Case	Age,	Renal dysfunction	Inflammation	Anasarca	Thrombocytopenia
1-1	61	17	13	20	41
1-2	70	38	26	66	73
2	68	12	10	93	39
3	17	4	21	24	0
4	71	7	36	33	46
5	52	6	31	10	46
6-1	61	6	22	22	68
6-2	62	2	13	4	30
7	50	16	17	33	63
Mean $\pm$ SD	56.9 $\pm$ 16.6	12.0 $\pm$ 11.1	21.0 $\pm$ 8.8	33.9 $\pm$ 28.3	45.1 $\pm$ 22.2
Median [IQR]	61.0 [51.0–68.0]	7.0 [6.0–16.0]	21.0 [13.0–26.0]	24.0 [20.0–33.0]	46.0 [39.0–63.0]

Recovery of renal function: The first day on which serum creatinine showed a sustained downward trend from its peak value.

Recovery of systemic inflammation: The day the C-reactive protein (CRP) level returned to the normal range.

Recovery of anasarca: The day body weight and/or abdominal circumference began to show a sustained decrease.

Recovery from thrombocytopenia: The day the platelet count reached $\geq 50 \times 10^3/\mu\text{L}$ on a sustained basis without platelet transfusion.

Thrombocytopenia was defined as a platelet count of $< 100 \times 10^3/\mu\text{L}$, with recovery defined as $\geq 50 \times 10^3/\mu\text{L}$. Time to recovery = 0 indicates a case in which the platelet count never fell below $50 \times 10^3/\mu\text{L}$.

SD: Standard Deviation; IQR: interquartile range, 25%–75%.

the early phase after treatment initiation and were discontinued within several days to one week. In cases with persistent or refractory anasarca, pleural drainage (Cases 1-1, 1-2, 2 (complicated by empyema), and 4) and peritoneal drainage (Cases 1-1, 1-2, 2, and 4) were performed as adjunctive supportive measures.

No fatal cases occurred during the observation period, and all patients survived to hospital discharge. Infectious complications were observed in four treatment courses, excluding preemptive therapy for cytomegalovirus antigenemia, and were associated with longer hospital stays (Table 1).

3.2. Time to recovery

Table 2 shows the time to improvement or recovery of individual clinical parameters, including renal function, systemic inflammation, anasarca and thrombocytopenia. Among the nine treatment courses, the time to recovery for each clinical domain was as follows (median [IQR]):

- Renal dysfunction (sustained decrease in serum creatinine): 7.0 days (IQR: 6.0–16.0),
- Systemic inflammation (CRP normalization): 21.0 days (IQR: 13.0–26.0),
- Anasarca (persistent weight reduction): 24.0 days (IQR: 20.0–33.0),
- Thrombocytopenia (sustained platelet count $\geq 50 \times 10^3/\mu\text{L}$ without transfusion): 46.0 days (IQR: 39.0–63.0).

Although thrombocytopenia was defined as a platelet count of $< 100 \times 10^3/\mu\text{L}$, the improvement point for the platelet count was set at $\geq 50 \times 10^3/\mu\text{L}$. Therefore, in Case 4, where the platelet count did not fall below $50 \times 10^3/\mu\text{L}$ during the clinical course, the time to recovery from thrombocytopenia was recorded as day 0.

As shown in Figure 1A, statistical comparison using the Wilcoxon signed-rank test with Bonferroni correction demonstrated that the time to recovery of renal dysfunction was significantly shorter than that of anasarca and thrombocytopenia ($p < 0.05$). No significant differences were observed for systemic inflammation after correction. Figure 1B presents the cumulative incidence of recovery for each clinical parameter using cumulative recovery curves. The plots highlight that thrombocytopenia and anasarca exhibited slower recovery than renal dysfunction and systemic inflammation, with thrombocytopenia showing the most delayed median recovery and anasarca displaying greater interindividual variability, supporting the notion that recovery kinetics differ among affected organ systems in TAFRO syndrome. Sensitivity analyses using alternative platelet thresholds (≥ 30 , ≥ 40 , and $\geq 100 \times 10^3/\mu\text{L}$) yielded similar results, with thrombocytopenia remaining the most delayed domain (Supplementary Table S1). Subgroup analysis excluding TCZ-treated courses ($n = 7$), performed to minimize the potential impact of IL-6 blockade on CRP normalization, showed a similar recovery sequence, with renal dysfunction improving first and thrombocytopenia last, while anasarca

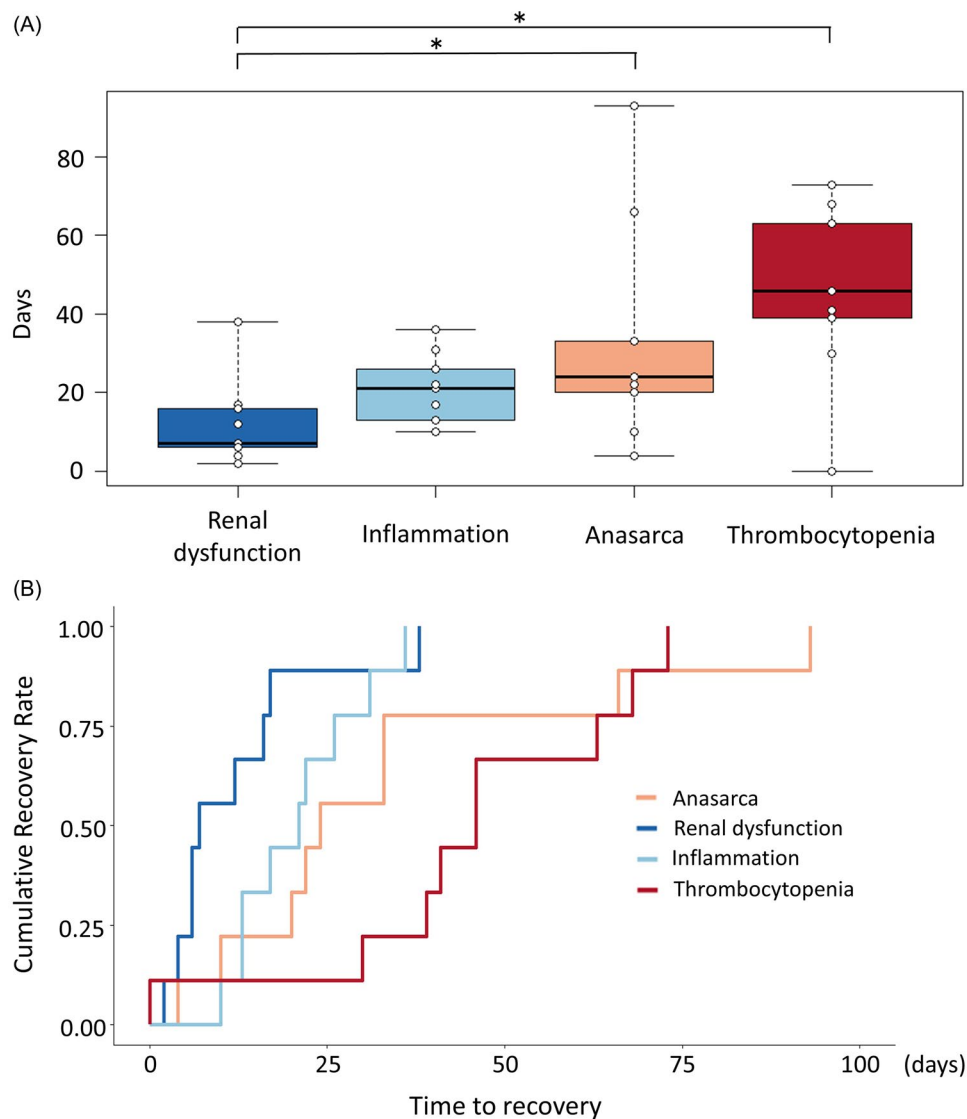


Figure 1. Recovery time and cumulative incidence of recovery for the clinical parameters. (A) Boxplots comparing the recovery times of renal dysfunction, systemic inflammation, anasarca, and thrombocytopenia, as defined in the Methods section. Statistical analysis was performed using the Wilcoxon signed-rank test with Bonferroni correction. $*p < 0.05$. (B) Cumulative recovery curves showing the cumulative incidence of recovery for each parameter based on the predefined definitions.

also tended to recover later than renal dysfunction; however, no pairwise comparisons reached statistical significance after Bonferroni correction, likely due to limited statistical power (Supplementary Figure S2). No significant correlations were observed between serum IL-6 or VEGF levels and the time to recovery in any clinical domain (Supplementary Figure S3).

4. Discussion

TAFRO syndrome is a rare systemic inflammatory disorder with a rapidly progressive course and high clinical severity. Due to its low prevalence and heterogeneity, there are limited data on its natural history, especially with respect to the organ-specific trajectories of recovery. In this retrospective case series of seven patients (nine treatment courses), we investigated the temporal patterns of recovery in four major clinical domains: renal dysfunction, systemic inflammation, anasarca, and thrombocytopenia.

The present cohort consisted of seven patients with TAFRO syndrome, including nine treatment courses, all of whom fulfilled the diagnostic criteria for TAFRO syndrome or iMCD-TAFRO based on comprehensive clinical assessment. At baseline, all patients exhibited systemic inflammation, renal dysfunction of varying severity, thrombocytopenia, and anasarca, reflecting high disease activity. Mild elevation of serum IgG levels was observed in Cases 2, 4, and 6; anti-SS-A antibodies were positive in Cases 1 and 2, and a direct Coombs test was positive in Case 6 (Table 1). In Case 1, anti-SS-A antibody positivity was noted in the absence of documented sicca symptoms, and a labial salivary gland biopsy was not performed. In Case 2, anti-SS-A and anti-SS-B antibodies were positive; however, the labial biopsy demonstrated only Greenspan grade 2 changes, and sicca manifestations were not clearly documented. Accordingly, Sjögren's disease was considered unlikely in both cases. Notably, anti-SS-A antibody positivity has been reported in patients with TAFRO syndrome even in the absence of overt autoimmune disease [6]. In Case 6, anemia, a positive direct Coombs test, and splenomegaly were observed; however, there was no laboratory evidence of hemolysis, including decreased haptoglobin or elevated lactate dehydrogenase and bilirubin levels. The anemia was therefore considered consistent with anemia of chronic inflammation, whereas the splenomegaly was attributable to TAFRO syndrome. Although lymph node biopsy was not available in Case 4, the overall clinical course, laboratory findings, and exclusion of alternative diagnoses were consistent with TAFRO syndrome. All treatment courses included glucocorticoids as initial therapy, followed by additional immunosuppressive agents or biologics according to disease severity and clinical response. Supportive interventions, including renal replacement therapy and drainage procedures, were implemented in selected cases during the acute phase. Importantly, these interventions were not used as criteria for defining recovery in each clinical domain; transient changes immediately following dialysis or drainage were excluded, and recovery was defined based on sustained improvement not attributable to these procedures.

Our findings revealed a clear disparity in the timing of organ recovery. Specifically, renal function and systemic inflammation, as reflected by serum creatinine and CRP levels, improved relatively early after treatment initiation. In contrast, anasarca and thrombocytopenia tended to show delayed recovery, with thrombocytopenia often requiring the longest duration. This observation highlights the necessity of interpreting the treatment response in TAFRO syndrome using a domain-specific timeline rather than a single global measure. To our knowledge, such organ-specific recovery kinetics have not been systematically evaluated in patients with TAFRO syndrome. To further elucidate these differential recovery kinetics, we next discuss the recovery trajectories of individual clinical domains.

Among the four clinical domains analyzed in this study, thrombocytopenia demonstrated the slowest and most variable recovery trajectory. Platelet recovery was defined as a sustained count of $50 \times 10^3/\mu\text{L}$, representing a clinically meaningful level associated with reduced bleeding risk and hematologic stabilization. Sensitivity analyses using alternative platelet thresholds (≥ 30 , ≥ 40 , and $\geq 100 \times 10^3/\mu\text{L}$) yielded similar temporal trends across the platelet definitions, indicating that the delayed recovery of thrombocytopenia was not dependent on the predefined cutoff (Supplementary Table S1). This finding is consistent with previous reports describing prolonged platelet recovery in patients with TAFRO syndrome, even after apparent control of systemic inflammation [7,8]. Notably, a recent single-center case series reported that delayed platelet recovery was not associated with adverse survival outcomes and suggested caution against intensifying immunosuppressive therapy solely to accelerate platelet recovery. In conjunction with our organ-specific recovery analysis, these findings support the interpretation that persistent thrombocytopenia represents a characteristic feature of the convalescent phase of TAFRO syndrome rather than an indicator of ongoing disease activity or treatment failure [8]. Bone marrow findings in TAFRO syndrome are characterized by increased megakaryocytes, frequently accompanied by varying degrees of reticulin fibrosis. However, these pathological features are heterogeneous and not universally present. A previous case series reported reticulin fibrosis in only a subset of patients, whereas atypical or dysmorphic megakaryocytes were consistently observed [3,9]. In the present study, bone marrow biopsy demonstrated megakaryocytosis in all cases, supporting the notion that impaired platelet recovery is unlikely to result from a simple quantitative failure of megakaryopoiesis. Rather, these observations suggest that delayed platelet recovery in TAFRO syndrome may be driven less by irreversible structural fibrosis and more by qualitative dysregulation of

megakaryocyte function. In addition, immune-mediated mechanisms may partially contribute to thrombocytopenia. Platelet-associated IgG (PA-IgG) was positive in three treatment courses in our cohort, suggesting that an immune thrombocytopenia-like mechanism could contribute to platelet reduction in a subset of patients. However, the frequent absence of PA-IgG indicates that thrombocytopenia in TAFRO syndrome cannot be fully explained by classical immune thrombocytopenia alone, and instead likely reflects a complex interplay between immune-mediated platelet destruction and ineffective platelet production under persistent immune dysregulation. Collectively, these findings indicate that prolonged thrombocytopenia in TAFRO syndrome is not simply a consequence of ongoing systemic inflammation, but rather reflects delayed restoration of effective megakaryopoietic homeostasis. In this context, thrombopoietin receptor agonists (TPO-RAs) were used as temporary adjunctive therapy and were successfully discontinued after platelet recovery in selected cases in our cohort. Although not curative, TPO-RAs may serve as valuable adjunctive options to provide hematologic support during the prolonged hematologic convalescence phase.

Beyond hematologic manifestations, another notable finding in this study was the delayed resolution of anasarca, which often persisted despite early improvement in renal function and normalization of systemic inflammatory markers. This dissociation suggests that mechanisms underlying fluid retention and capillary leakage in TAFRO syndrome may not fully overlap with those driving systemic inflammation, as assessed by serum biomarkers such as CRP. Although elevated levels of IL-6 and VEGF are well-recognized features of TAFRO syndrome, we did not observe a clear association between serum IL-6 or VEGF levels at baseline and the duration of anasarca in our cohort ([Supplementary Figure S1, S3C,G](#)). These findings imply that suppression of IL-6-mediated systemic inflammation, including through IL-6 receptor blockade, may be insufficient to promptly restore vascular homeostasis in some patients. Recent studies have further identified the involvement of additional cytokines and chemokines beyond IL-6 and VEGF, including CXCL10 (interferon- γ -induced protein 10), CXCL13, IL-10, and IL-23, particularly during disease flares in iMCD-TAFRO [10–13]. Moreover, immunophenotyping and transcriptomic analyses have revealed activation of multiple immune pathways, such as JAK/STAT, PI3K/Akt/mTOR, and type I interferon signaling, across diverse immune cell populations [14–16]. Rather than implicating a single dominant pathway, these observations support a model of multilayered and spatially heterogeneous immune activation contributing to sustained endothelial dysfunction and increased vascular permeability. Taken together, persistent anasarca in TAFRO syndrome may reflect delayed recovery of endothelial integrity and immune-mediated vascular regulation that may normalize more slowly than systemic inflammatory markers. From a clinical perspective, the delayed resolution of anasarca underscores the need for cautious interpretation of residual fluid retention, as premature escalation of immunosuppressive therapy may increase the risk of treatment-related complications.

The organ-specific recovery kinetics observed in this study have important implications for the clinical management of TAFRO syndrome. Although high-dose glucocorticoids remain the cornerstone of initial therapy, early normalization of inflammatory markers does not necessarily indicate comprehensive disease control. While TAFRO syndrome is often classified as a subtype of idiopathic multicentric Castleman disease (iMCD), increasing evidence suggests that it represents a distinct clinicopathological entity [17]. Consistent with this distinction, IL-6 inhibitors, which are highly effective in many cases of iMCD, are not universally effective in TAFRO syndrome [18]. The dissociation between inflammatory improvement and delayed recovery of thrombocytopenia or anasarca observed in our cohort supports the involvement of immunologic pathways beyond IL-6 signaling, including T- and B-lymphocyte activation [19–22]. In our series, remission was ultimately achieved through iterative and adaptive adjustment of glucocorticoids combined with immunosuppressive or immunomodulatory agents, supporting a multimodal treatment approach tailored to disease severity and dominant clinical manifestations. Importantly, delayed recovery of thrombocytopenia or anasarca may be interpreted within the context of the natural history of TAFRO syndrome rather than as an immediate indicator of refractory disease. Over interpretation of these persistent manifestations may lead to unnecessary escalation of immunosuppressive therapy and increase the risk of opportunistic infections, a critical challenge in TAFRO syndrome management. Indeed, several patients in our cohort required prolonged hospitalization due to infectious complications ([Table 1](#)), and prior

reports have documented infection-related mortality during treatment [23–30]. Under these circumstances, a balanced approach that avoids excessive immunosuppression while incorporating supportive or adjunctive strategies targeting alternative mechanisms may be warranted during the recovery phase.

This study has several limitations. First, the retrospective design and small sample size limit the generalizability of our findings to other patient populations. Second, no fatal cases were included in the present cohort, which may introduce survivorship bias. Third, some clinical parameters such as IL-6 and VEGF levels were not available in all patients, precluding a comprehensive analysis of cytokine dynamics. Finally, the definitions of recovery were operational and based on selected clinical parameters rather than validated composite indices, and alternative definitions might yield different timelines; however, sensitivity analyses using alternative platelet thresholds showed consistent patterns. Further multicenter studies with standardized assessment protocols are warranted to validate our observations.

5. Conclusions

In conclusion, recovery trajectories in TAFRO syndrome differ substantially across affected organ systems, with thrombocytopenia showing the most delayed median recovery and anasarca demonstrating variable resolution compared with inflammatory or renal parameters. These findings highlight the importance of a domain-specific interpretation of treatment response and an understanding of the natural history of the disease. Recognition of differential recovery timelines may help clinicians balance disease control with treatment-related risks and guide more individualized management strategies for TAFRO syndrome.

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Authors contributions

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Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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