# TAFRO syndrome without pathological evidence consistent with Castleman disease: a subtype of TAFRO or a distinct disease entity?

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## Introduction

- Idiopathic TAFRO syndrome, characterized by **T**hrombocytopenia, **A**nasarca, **F**ever, **R**eticulin myelofibrosis, **R**enal dysfunction, and **O**rganomegaly, was primarily considered a distinct subtype of idiopathic multicentric Castleman disease (iMCD-TAFRO). Patients often experience severe cytokine storm, leading to multiorgan failure if not treated adequately and promptly. According to the Castleman Disease Collaborative Network (CDCN), the diagnostic criteria for iMCD-TAFRO require pathological evidence consistent with Castleman disease (CD). However, obtaining lymph node biopsies is challenging for TAFRO patients **(TAFRO without pathological evidence, TAFRO-w/op-iMCD)**[1] due to the unapparent lymphadenopathy and high-risk of bleeding caused by thrombocytopenia. Even with significant effort, biopsies may not yield conclusive pathological findings consistent with iMCD spectrum **(TAFRO-w/o-iMCD)**[1].
- **Without a definite pathological diagnosis** of Castleman disease for patients with TAFRO-w/o-iMCD and TAFRO-w/op-iMCD, **treatment might be delayed** which would bring poor diagnosis.
- Previous studies demonstrated that **TAFRO-w/op-iMCD** patients showed no significant differences in clinical presentation, laboratory findings, and treatment efficacy compared with iMCD-TAFRO patients and **could be regarded as a subtype of TAFRO syndrome**. However, it remains unclear **whether TAFRO-w/o-iMCD should be treated as a subtype of TAFRO syndrome**.

## Methods

- This retrospective, single-center study included patients diagnosed with iMCD-TAFRO and TAFRO-w/o-iMCD from May 2015 to Jun 2024. The diagnostic criteria for TAFRO syndrome require all three major categories and at least two of four minor categories and failing to satisfy any of the suggested exclusion criteria[2].
- Patients with TAFRO syndrome were categorized into iMCD-TAFRO, TAFRO-w/op-iMCD, and TAFRO-w/o-iMCD and **we included patients with iMCD-TAFRO and TAFRO-w/o-iMCD**. Treatment response (symptomatic response and biochemical response) was evaluated according to the CDCN guidelines, with **primary outcomes** being response rates at 3 months, 6 months, and the best overall response. **Secondary outcomes** included 3-year estimated progression-free survival (PFS), overall survival (OS) rates, and 3-month mortality rate.

## Results

- A total of 61 patients were included(50 iMCD-TAFRO and 11 TAFRO-w/o-iMCD).
- Both groups showed no significant differences in **clinical presentations** (fatigue, anasarca, fever, organomegaly, and skin involvement) and **laboratory data** (including hemoglobin, platelets, creatinine, hypersensitive C-reactive protein, and interleukin-6).
- Each group had one patient who achieved spontaneous remission, while the remaining 59 patients were **treated with iMCD-targeted strategies addressing cytokine storm.**
  - With a median follow-up time of 21.4 (range, 0.5-107.0) months, there were **no significant differences** between iMCD-TAFRO to TAFRO-w/o-iMCD patients in terms of the 3-month response rate (72.1% vs. 88.9%, P=0.525), 6-month response rate (70.0% vs. 83.3%, P=0.849), and best overall response rate (77.6% vs. 90.0%, P=0.645).
  - The 3-month mortality rate (12.0% vs. 0%, P=0.515), estimated 3-year PFS rate (65.8% vs. 90.0%, log-rank P=0.163), and estimated 3-year OS rate (77.0% vs. 100%, log-rank P=0.145) **were also not significantly different**.
- Decreased eGFR level (< 60ml/min/1.73m2) was associated with an increased risk of disease progression (OR=5.556, 95%CI: 1.653-18.672, p=0.006) in our cohort.

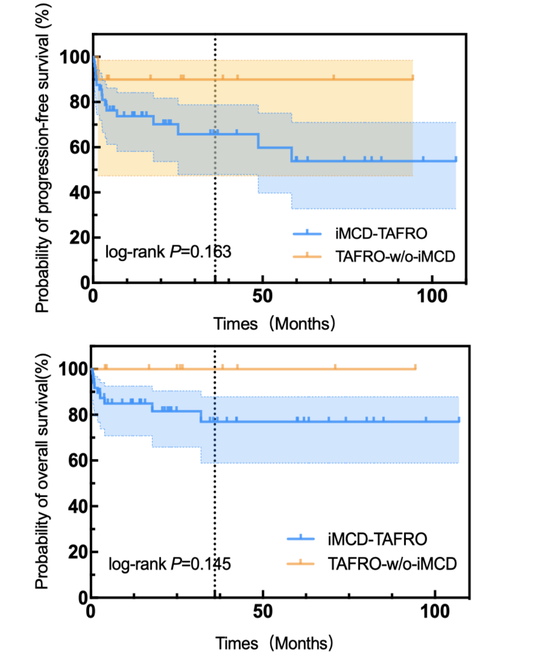


**Fig 1.** Kaplan-Meier plots of PFS and OS in patients with iMCD-TAFRO (n=49) and TAFRO-w/o-iMCD (n=10).

**Conclusion** iMCD-TAFRO and TAFRO-w/o-iMCD patients could be considered as the same disease entity and be treated promptly, targeting the cytokine storm using similar treatment strategies.

**Reference**: [1] Am J Hematol 2021, 96:1241-1252. [2] Int J Hematol 2020, 111:155-158).