Predictors of steroid-refractory immune checkpoint inhibitor associated myocarditis

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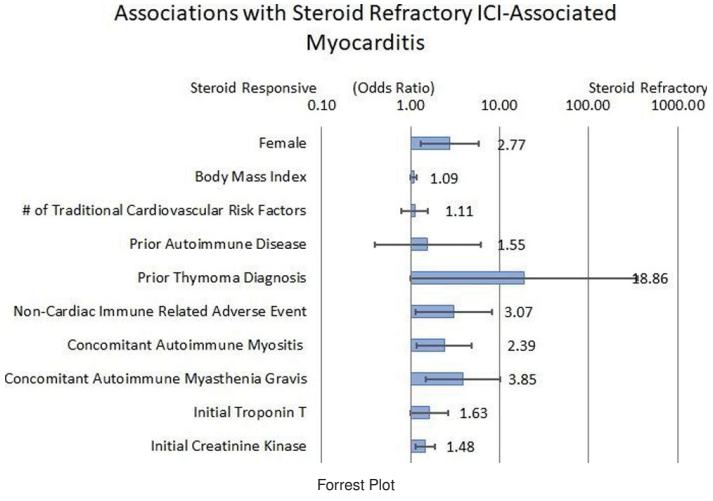
Background/Introduction: Immune checkpoint inhibitor (ICI)-associated myocarditis has a high mortality rate of approximately 50%. Clinical decompensation often occurs despite first-line treatment with corticosteroids. Factors associated with steroid failure are currently unknown.

Purpose: To identify predictors of steroid failure in patients with ICI-associated myocarditis.

Methods: We developed a web-based registry to collect and study 157 cases with clinical manifestations of ICI-associated myocarditis across 16 countries. Steroid failure was defined as patients who were escalated to immunomodulators after $\geq$1mg/kg daily dose of prednisone or had in-hospital death due to myocarditis despite $\geq$1mg/kg daily dose of prednisone. Steroid response was defined as all other patients treated with steroids without escalation to immunomodulators and without death due to myocarditis. A multivariate logistic model accounting for age and sex was used to predict association with steroid failure.

Results: Compared to steroid responsive cases, steroid failure was more likely to result in fulminant myocarditis (56.7% vs 19.6%, OR=5.37 [2.62–10.98] p<0.001) and all-cause in-hospital mortality (49.1% vs 12.9%, OR=6.50 [2.86–14.73] p<0.001) with shorter time from presentation to death (27.5 vs 43.0 days HR: 2.56 [1.45–4.50] p=0.001). When adjusting for age and sex, cases were more likely to be steroid-refractory if they were female (46.7% vs 30.1%, OR=2.77 [1.31–5.85] p=0.007), higher body mass index (27.2 vs 22.0, OR=1.09 [1.01–1.18] p=0.012), had higher intake creatine kinase (2800.5 vs 528.0 U/L, OR=1.48 [1.14–1.90] p=0.003) had higher intake troponin T (1.40 vs 0.25 ng/mL OR=1.63 [1.00–2.64] p=0.049), or had one or more concomitant non-cardiac immune-related adverse event (90.0% vs 74.2%, OR=3.10 [1.14–8.25] p<0.026). The only immune-related adverse events independently associated with steroid failure in myocarditis were myasthenia gravis-like syndrome (26.7% vs 8.2%, OR=3.84 [1.47–10.10] p=0.006) and myositis (45.0% vs 24.7%, OR=2.38 [1.16–4.92] p=0.018). Steroid failure was not significantly associated with cardiovascular or autoimmune history but was associated with a history of thymoma (12.0% vs 2.6%, OR=18.86 [0.10–356.7] p=0.05)

Conclusion(s): Features such as female sex, high body mass index, and pre-existing thymoma as well as findings of elevated cardiac biomarkers and other non-cardiac immune-related adverse events – particularly myositis and myasthenia gravis-like syndrome – may represent a steroid-refractory phenotype of ICI-associated myocarditis. These results suggest that a multidisciplinary approach to diagnosing concomitant non-cardiac immune related adverse events is key to risk-stratifying ICI-associated myocarditis.



Forrest Plot