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Coronary artery disease and revascularization associated with immune checkpoint blocker myocarditis: Report from an international registry

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Author contributions

All co-authors and collaborators performed data collection. JN, PG and SH performed analysis. JM and JES designed and supervised the research. JN, PG, JM and JES wrote the paper. All authors provided critical review to this work.

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Abstract

***Purpose*:** Immune checkpoint blocker (ICB) associated myocarditis (ICB-myocarditis) may present similarly and/or overlap with other cardiac pathology including acute coronary syndrome presenting a challenge for prompt clinical diagnosis.

***Methods*:** An international registry was used to retrospectively identify cases of ICB-myocarditis. Presence of coronary artery disease (CAD) was defined as coronary artery stenosis >70% in patients undergoing coronary angiogram.

***Results*:** Among 261 patients with clinically suspected ICB-myocarditis who underwent a coronary angiography, CAD was present in 59/261 patients (22.6%). Coronary revascularization was performed during the index hospitalisation in 19/59 (32.2%) patients. Patients undergoing coronary revascularization less frequently received steroids administration within 24 h of admission compared to the other groups (p = 0.029). Myocarditis-related 90-day mortality was 9/17 (52.7%) in the revascularised cohort, compared to 5/31 (16.1%) in those not revascularized and 25/156 (16.0%) in those without CAD (p = 0.001). Immune-related adverse event-related 90-day mortality was 9/17 (52.7%) in the revascularized cohort, compared to 6/31 (19.4%) in those not revascularized and 31/156 (19.9%) in no CAD groups (p = 0.007). All-cause 90-day mortality was 11/17 (64.7%) in the revascularized cohort, compared to 13/31 (41.9%) in no revascularization and 60/158 (38.0%) in no CAD groups (p = 0.10). After adjustment of age and sex, coronary revascularization remained associated with ICB-myocarditis-related death at 90 days (hazard ratio [HR] = 4.03, 95% confidence interval [CI] 1.84–8.84, p < 0.001) and was marginally associated with all-cause death (HR = 1.88, 95% CI, 0.98–3.61, p = 0.057).

Conclusion: CAD may exist concomitantly with ICB-myocarditis and may portend a poorer outcome when revascularization is performed. This is potentially mediated through delayed diagnosis and treatment or more severe presentation of ICB-myocarditis.

Keywords

Immune checkpoint blockers; Immune-related adverse events; Myocarditis; Acute coronary syndrome; Coronary revascularization

1. Introduction

Immune checkpoint blockade (ICB) has revolutionised cancer therapy [1,2]. Since ipilimumab was authorised for use in 2011, additional ICB has been approved for an ever-growing number of malignancies leading to improved survival [1,2]. Balance between the activation of the innate immune system is necessary to effectively treat the cancer while ideally preventing toxicities known as immune-related adverse events (irAE) [2]. ICB-myocarditis can present with a wide spectrum of disease severity, including pseudo-acute coronary syndrome (ACS) [3], while rare, fulminant myocarditis is associated with high mortality [4,5]. Treatment of ACS and ICB-myocarditis (Fig. 1) mainly relying on prompt start of immunosuppressant differs considerably [3,6–8]. Recently, we took care of an ICB-myocarditis case which initially appeared to be ACS, until the patient decompensated following percutaneous coronary intervention, and steroids were ultimately started 2 days later, and eventual cardiac biopsy confirming ICB-myocarditis (Fig. 1). This prompted our further examining the concomitance of coronary artery disease (CAD) with ICB-myocarditis and the implications of revascularization and outcomes for such patients; data are currently lacking with this question. We utilised an international ICB-myocarditis registry, previously described [9,10], to better understand the outcomes of patients presenting with clinically suspected ICB-myocarditis and the effect of undergoing acute coronary revascularization on outcomes.

2. Methods

2.1. Study population

A retrospective online HIPPA (Health Insurance Portability and Accountability Act) compliant registry spanning 57 institutions across 11 countries (NCT04294771) was used to identify 261 cases of suspected ICB-myocarditis [9] who received a coronary angiogram through August 31, 2021.

Baseline demographic, presenting characteristics, including the presence of significant CAD defined as stenosis ≥70% of a coronary artery, as well as outcomes were collected by site-specific collaborators. Indication for coronarography as well as coronary revascularization strategy with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was left to the discretion of contributing physician and performed during index hospitalisation. Primary outcome of interest was ICB-myocarditis mortality, and secondary outcomes were irAE-related mortality and all-cause mortality at 90 days, as classified by the treating physician. IrAE-related death included myocarditis, myositis leading eventually to respiratory failure [11,12] and other organ dysfunction due to immune overactivation [13]. Upon acceptance of participating in this registry, contributors were specifically asked to focus on adjudicating these latter causes of death, as much as possible prospectively; or if impossible, through retrospective medical files analysis. Laboratory values were standardised to institutional upper limit of normal (ULN). Steroid dose was standardised to equivalent in milligrams of intravenous methylprednisolone.

2.2. Statistical analysis

Categorical variables were described as number (%), and continuous variables were described as median (25%–75%, interquartile range [IQR]). Categorical and continuous variables were compared using χ^2 and Kruskal–Wallis tests, respectively. Cumulative incidence curves were presented and compared using the log-rank test for all-cause death, and Gray test for irAE-related and ICB myocarditis-related death. The clinical impact of the presence of CAD and coronary revascularization was determined using a Cox model for all-cause death and cause-specific hazard regression for irAE-related and ICB myocarditis-related death adjusted on age and sex. Adjusted hazard ratio (aHR) with 95% confidence interval (CI) was reported. P-value<0.05 was considered significant. Statistics were performed with R-v4.0.5. As this was a retrospective analysis, data that were missing from the registry required censorship during final statistical analysis.

3. Results

Of the 474 cases included in the ICB-myocarditis registry, 261 (55.1%) underwent coronary angiography. There was no difference in terms of age between those with and without coronary angiography (69.0 [60.8–78.0] vs. 69.0 [61.0–76.0], respectively, p = 0.37) and female prevalence (52/170 [30.5%] vs. 91/261 [34.7%], respectively, p = 0.45). CAD was found in 59/261 (22.6%), and coronary revascularization was performed in 19/59 (32.3%) including 16 cases of PCI and 3 of CABG. The patients who underwent angiography had received 2 (1–4) doses of ICB and were admitted 40 (24–87) days

following ICB start for various cancers (detailed in Table 1). Patients who underwent revascularization were older, more frequently male, had more pre-existing cardiovascular risk factors and currently taking cardio-metabolic protective drugs compared to those who did not undergo revascularization (Table 1). Admission symptoms, troponin levels, echocardiography (wall motion abnormalities and left ventricular ejection fraction) and electrocardiogram did not show any statistically significant difference upon presentation among patients ultimately undergoing urgent coronary revascularization versus patients with CAD but no revascularization and patients with no CAD (Table 1). Peak troponin circulating levels were higher among patients undergoing coronary revascularization (median = 296 times upper limit of the normal, ULN) versus CAD but no revascularization (37 times ULN) and no CAD groups (67 times ULN, p = 0.009).

The proportion of patients treated with steroid administration in the first 24 h of admission was significantly lower among patients undergoing coronary revascularization (43.8%) compared to CAD but no revascularization (80.5%) and no CAD (63.9%) groups (p = 0.029). The median dose of initial steroid dose (standardised to intravenous methylprednisone equivalent) for those with coronary intervention was 160 mg, not statistically significant (p = 0.32) compared to the CAD but no revascularization (750 mg) and no CAD groups (500 mg). Overall, 166/222 (74.8%) patients had either histological (biopsy or autopsy) or cardiac magnetic imaging confirmed myocarditis, with no difference between the three subgroups classified by CAD status (p = 0.65, Table 1). Concurrent association with other irAE including myositis, myasthenia-gravis like syndrome and hepatitis (overall: 35.2%, 38.7% and 20.3%, respectively) was similar between the three subgroups classified by CAD status (Table 1). A total of 63/261 (24%) patients developed a life-threatening cardiac arrhythmia.

Patients who underwent urgent revascularization required greater haemodynamic support as 50% required vasopressors or inotropes versus 15% in CAD but no revascularization groups and 24.7% in the no CAD groups (p = 0.017). Myocarditis-related 90-day mortality was 9/17 (52.7%) in the revascularized cohort, compared to 5/31 (16.1%) in those not revascularized and 25/156 (16.0%) in those without CAD (p = 0.001) (Fig. 2). IrAE-related 90-day mortality was 9/17 (52.7%) in the revascularized cohort, compared to 6/31 (19.4%) in those not revascularized and 31/156 (19.9%) in no CAD groups (p = 0.007) (Fig. 2). All-cause 90-day mortality was 11/17 (64.7%) in the revascularized cohort, compared to 13/31(41.9%) in no revascularization and 60/158 (38.0%) in no CAD groups (p = 0.10). After adjustment on age and sex, urgent coronary revascularization during index hospitalisation was associated with a significantly higher risk of irAE-related and myocarditis-related mortality at 90 days as compared to non-urgent coronary revascularization groups (i.e., CAD but no revascularization and no CAD), with aHR = 3.20 (95% CI = 1.49–6.85, p = 0.003) and aHR = 4.03 (95% CI = 1.84–8.84, p < 0.001), respectively, and was marginally more associated with all-cause death at 90 days, with aHR = 1.88 (95% CI = 0.98–3.61, p = 0.057) (Figure- 2).

4. Discussion

In this retrospective study of patients with clinically suspected ICB-myocarditis, the presence of concurrent ACS requiring urgent revascularization was associated with higher irAE and ICB-myocarditis-related mortality at 90 days and marginally with all-cause mortality versus patients having a significant CAD not requiring urgent revascularization and no CAD. There may be two potentially complementary explanations for our results. First, there was a delay in initial steroid administration in patients requiring revascularization with evidence that early administration of immunosuppressant has improved outcomes in patients with ICB-myocarditis [14]. As in the case detailed in the Fig. 1, such patients can be treated initially only for ACS, and ICB-myocarditis eventually being suspected after worsening of clinical status despite coronary revascularization. Additionally, and/or alternatively, there have been increasing reports that ICB can increase coronary plaque destabilisation and rupture potentially leading to acute thrombosis [15–18]. In animal models, the inhibited immune checkpoints downregulate the proatherogenic cytokines leading to plaque destabilisation, increasing the risk of plaque breakage and thrombus formation [19–21]. There have also been reports of vasculitis [4], which along with plaque destabilisation can be viewed as a greater degree of immune activation affecting multiple organs and systems, which has been related to greater mortality [13]. Consequently, patients undergoing coronary revascularization in our cohort potentially suffered from both a potentially more intense myocarditis as well as myocardial ischaemia, leading to higher myocardial damage as observed with an elevated troponin level, and thus, increased mortality [22].

From a diagnostic perspective, discriminating ICB-myocarditis from myocardial infarction may be guided by the following discriminative features. ICB-myocarditis is often associated with other irAE, mainly including myositis, myasthenia-gravis syndrome and hepatitis while those associations are not expected in regular myocardial infarction [3,4]. Cardiac MRI display specifically subendocardial to transmural late-gadolinium enhancement (LGE) in a concordant coronary territory in regular myocardial infarction due to coronary occlusion, while LGE is mostly diffuse sub-epicardial, mid-myocardial or absent in ICB-myocarditis [3,23,24]. Though, subendocardial LGE features have also been reported in ICB-myocarditis [24]. On pathology, ICB-myocarditis is characterised by myocardial infiltration of macrophages and lymphocytes with associated cardiomyocyte death, while cardiac infarction pathology shows neutrophil infiltration associated with post-ischaemic coagulative necrosis [25–27].

We acknowledge several limitations in this retrospective international analysis including imperfect completeness of data (~10–20% of missing data). Indication for coronary angiograms and interventions and cause of death outcomes were locally determined. Since these diagnoses were not centrally adjudicated, they are subject to heterogeneity and classification bias weakening any firm conclusion one could make of our findings. Consequently, our results should be considered as hypothesis generating. Additionally, as this is a new and evolving condition, our sample size and resulting statistical power remained limited, precluding for adjustment on multiple covariates of interest. Our results

must be confirmed in prospective studies, ideally also comparing outcomes to a control cancer population with known stable CAD started on ICB.

5. Conclusion

In the setting of clinically suspected ICB-myocarditis, CAD requesting coronary revascularization was associated with irAE-related and myocarditis-related death at 90 days. Those solely with coronary disease but no need for urgent revascularization had similar results as compared to those without coronary disease.

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Conflict of interest statement

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests: LL has served on the advisory board for Daiichi Sankyio, Senaca, Astra Zeneca and Servier, as an external expert for Astra Zeneca and received speakers' honoraria from Novartis and MSD. LL is receiving grants from the German Center for Cardiovascular Research (DZHK), German Reuter Foundation (DFG) LE3570/2–1; 3570/3–1 and grant 01KC2006B from the Federal Ministry for Education and Research (BMBF). DA received speakers' honoraria from BMS, Ipsen and participated to ad-boards from Sanofi and AstraZeneca. KT has received honoraria from Bristol Myers Squibb, Pfizer, Ono Pharmaceutical, Merck BioPharma, Bayer, and grants from Otsuka, Daiichi, Sankyo and Takeda. JM has served on advisory boards for Bristol Myers Squibb, Takeda, Regeneron, Audentes, Deciphera, Ipsen, Janssen, ImmunoCore, Boston Biomedical, Amgen, Myovant, Triple Gene/Precigen, Cytokinetics and AstraZeneca and supported by NIH grants (R01HL141466, R01HL155990, R01HL156021). JES have received consultancy fees from BMS, BeiGene, AstraZeneca, Novartis, and grants from BMS, Novartis, French Agence Nationale de la Recherche, Fondation Coeur et Recherche, Fédération Française de Cardiologie. All other authors have nothing to declare.

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References

[1]. Robert C A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun 2020;11(1):3801. [PubMed: 32732879]

[2]. Geraud A, Gougis P, Vozy A, et al. Clinical pharmacology and interplay of immune checkpoint Agents: a Yin-Yang balance. Annu Rev Pharmacol Toxicol 2021;61:85–112. [PubMed: 32871087]

[3]. Lehmann LH, Cautela J, Palaskas N, et al. Clinical strategy for the diagnosis and treatment of immune checkpoint inhibitor-associated myocarditis: a narrative review. JAMA Cardiol 2021;6(11):1329–37. [PubMed: 34232253]

[4]. Salem JE, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 2018;19(12):1579–89. [PubMed: 30442497]

[5]. Nguyen LS, Cooper LT, Kerneis M, et al. Systematic analysis of drug-associated myocarditis reported in the World Health Organization pharmacovigilance database. Nat Commun 2022;13(1):25. [PubMed: 35013204]

[6]. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42(14): 1289–367. [PubMed: 32860058]

[7]. Salem JE, Allenbach Y, Vozy A, et al. Abatacept for severe immune checkpoint inhibitor-associated myocarditis. N Engl J Med 2019;380(24):2377–9. [PubMed: 31189043]

[8]. Nguyen LS, Bretagne M, Arrondeau J, et al. Reversal of immune-checkpoint inhibitor fulminant myocarditis using personalized-dose-adjusted abatacept and ruxolitinib: proof of concept. J Immunother Cancer 2022;10(4).

[9]. Power JR, Alexandre J, Choudhary A, et al. Electrocardiographic manifestations of immune checkpoint inhibitor myocarditis. Circulation 2021;144(18):1521–3. [PubMed: 34723640]

[10]. Power JR, Alexandre J, Choudhary A, et al. Association of early electrical changes with cardiovascular outcomes in immune checkpoint inhibitor myocarditis. Arch Cardiovasc Dis 2022; 115(5):315–330. [PubMed: 35595646]

[11]. Allenbach Y, Anquetil C, Manouchehri A, et al. Immune checkpoint inhibitor-induced myositis, the earliest and most lethal complication among rheumatic and musculoskeletal toxicities. Autoimmun Rev 2020;19(8):102586. [PubMed: 32535094]

[12]. Johnson DB, Manouchehri A, Haugh AM, et al. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. J Immunother Cancer 2019;7(1):134. [PubMed: 31118078]

[13]. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol 2018;4(12):1721–8. [PubMed: 30242316]

[14]. Zhang L, Zlotoff DA, Awadalla M, et al. Major adverse cardiovascular events and the timing and dose of corticosteroids in immune checkpoint inhibitor-associated myocarditis. Circulation 2020;141(24):2031–4. [PubMed: 32539614]

[15]. Drobni ZD, Alvi RM, Taron J, et al. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. Circulation 2020;142(24):229–311.

[16]. Cautela J, Rouby F, Salem JE, et al. Acute coronary syndrome with immune checkpoint inhibitors: a proof-of-concept case and pharmacovigilance analysis of a life-threatening adverse event. Can J Cardiol 2020;36(4):476–81. [PubMed: 32144037]

[17]. Kondapalli L, Bottinor W, Lenneman C. By releasing the brakes with immunotherapy, are we accelerating atherosclerosis? Circulation 2020;142(24):2312–5. [PubMed: 33315491]

[18]. Tomita Y, Sueta D, Kakiuchi Y, et al. Acute coronary syndrome as a possible immune-related adverse event in a lung cancer patient achieving a complete response to anti-PD-1 immune checkpoint antibody. Ann Oncol 2017;28(11):2893–5. [PubMed: 28651328]

[19]. Bu DX, Tarrio M, Maganto-Garcia E, et al. Impairment of the programmed cell death-1 pathway increases atherosclerotic lesion development and inflammation. Arterioscler Thromb Vasc Biol 2011;31(5):1100–7. [PubMed: 21393583]

[20]. Lee J, Zhuang Y, Wei X, et al. Contributions of PD-1/PD-L1 pathway to interactions of myeloid DCs with T cells in atherosclerosis. J Mol Cell Cardiol 2009;46(2):169–76. [PubMed: 19056397]

[21]. Zhao TX, Mallat Z. Targeting the immune system in atherosclerosis: JACC state-of-the-art review. J Am Coll Cardiol 2019; 73(13):1691–706. [PubMed: 30947923]

[22]. Lippi G, Cervellin G. Cardiac troponin T versus cardiac troponin I for mortality risk prediction: is one biomarker better than the other? Clin Biochem 2020;78:40–1. [PubMed: 32035076]

[23]. Ederhy S, Fenioux C, Cholet C, et al. Immune checkpoint inhibitor myocarditis with normal cardiac magnetic resonance imaging: importance of cardiac biopsy and early diagnosis. Can J Cardiol 2021;37(10):1654–6. [PubMed: 33373722]

[24]. Ederhy S, Salem JE, Dercle L, et al. Role of cardiac imaging in the diagnosis of immune checkpoints inhibitors related myocarditis. Front Oncol 2021;11:640985. [PubMed: 34055610]

[25]. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016;375(18):1749–55. [PubMed: 27806233]

[26]. Champion SN, Stone JR. Immune checkpoint inhibitor associated myocarditis occurs in both high-grade and low-grade forms. Mod Pathol 2020;33(1):99–108. [PubMed: 31534205]

[27]. Pasotti M, Prati F, Arbustini E. The pathology of myocardial infarction in the pre- and post-interventional era. Heart 2006; 92(11):1552–6. [PubMed: 16621872]

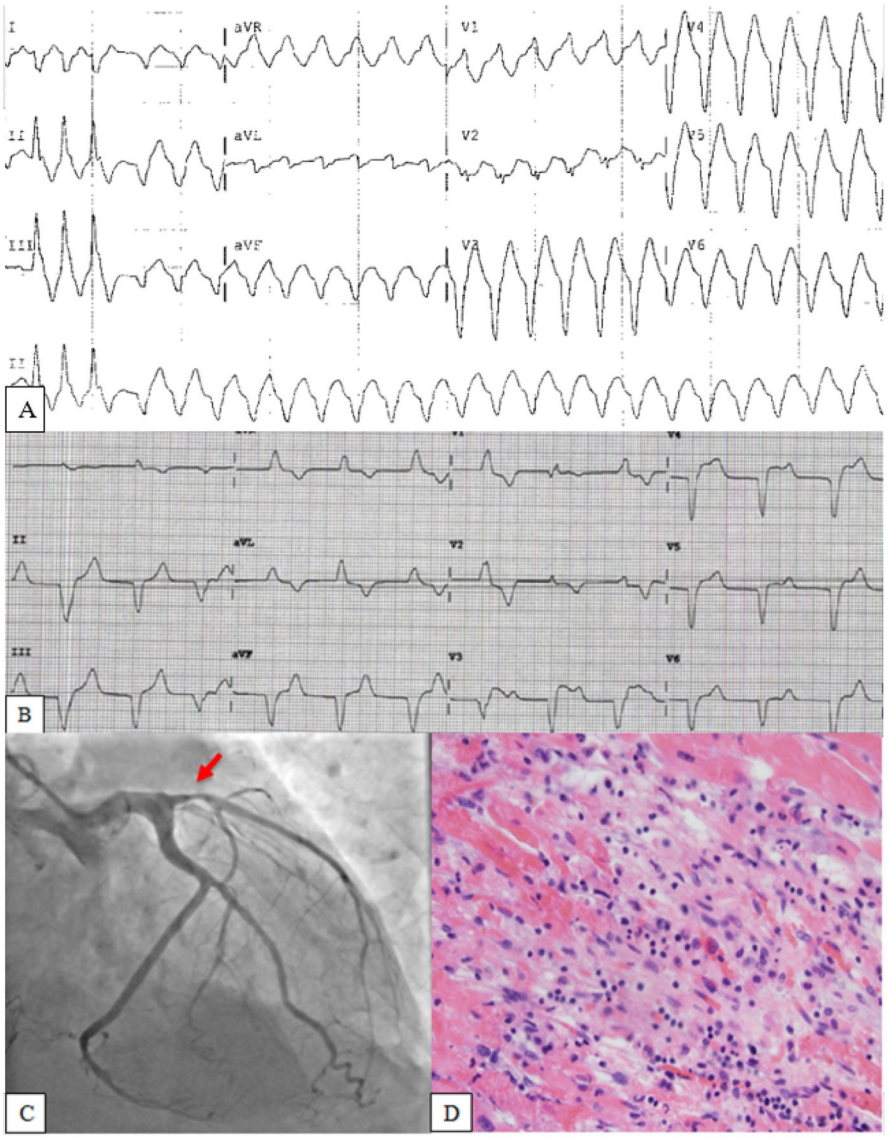

Fig. 1.

A 75-year-old male with hypertension, atrial fibrillation, metastatic renal cell carcinoma treated with ipilimumab and nivolumab most recently 4 days prior presented with palpitations and found to be in ventricular tachycardia (A), which converted to atrial fibrillation with ST segment elevations in leads V3–V6 (B). Urgent coronary angiogram was performed demonstrating an 80% left anterior descending blockage (red arrow, C), which was treated with percutaneous coronary intervention (PCI) with a drug-eluting stent. Transthoracic echocardiogram demonstrated apical hypokinesis and dilated right ventricle, with 50–55% ejection fraction. The day after the intervention, the patient developed wide complex tachycardia treated by lidocaine bolus, which evolved to complete atrioventricular heart block associated with shock requiring vasopressor support, continuous renal replacement therapy and intubation for hypoxic respiratory failure. He was then started on 100 mg of intravenous methylprednisolone, ultimately increased to 1000 mg

methylprednisolone for 3 days. Troponin-I peeked 2 days after initial PCI at 40.46 ng/ml (upper limit of normal 0.03 ng/ml). Endomyocardial biopsy on Day 5 was consistent with lymphocytic myocarditis (D). With no clinical improvement, the patient's family decided to transition to comfort care measures and the patient was extubated and passed away 7 days after initial presentation.

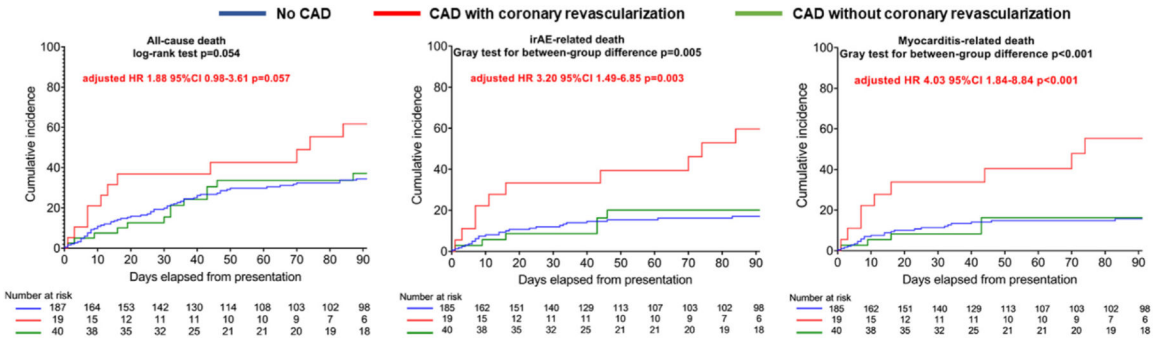

Fig. 2.

Cumulative incidence of event curves by presence of coronary artery disease and revascularization assessing myocarditis-related death, irAE-death, and all-cause death at 90 days. Adjusted hazard ratio (aHR) and confidence interval (CI) represent the association of coronary revascularization (vs. no revascularization) adjusted on age and sex with the outcome of interest.

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Table 1

Demographics, baseline characteristics based on presence of coronary artery disease and revascularization.

	No significant CAD [n = 202]	CAD without coronary intervention [n = 40]	CAD and coronary intervention [n = 19]	p-value
Age at hospital admission (years)	67.0 (59.0–75.0) [n = 200]	76.0 (62.0–78.2) [n = 40]	75.0 (70.0–77.5) [n = 19]	**<0.001**[a,c]
Female	82/202 (40.6%)	5/40 (12.5%)	2/19 (10.5%)	**<0.001**[a,c]
Medical history				
Coronary artery disease	24/189 (12.7%)	20/40 (50.0%)	11/19 (57.9%)	**<0.001**[a,c]
Heart failure	13/183 (7.1%)	4/39 (10.3%)	3/17 (17.6%)	0.29
Cardiovascular risk factors				
Body mass index	25.1 (21.4–28.1) [n = 176]	27.7 (24.5–29.6) [n = 40]	29.1 (25.0–31.3) [n = 19]	**0.004**[a,c]
Dyslipidemia	65/181 (35.9%)	24/40 (60.0%)	13/19 (68.4%)	**0.001**[a,c]
Diabetes	41/181 (22.7%)	15/39 (38.5%)	9/19 (47.4%)	**0.016**[a,c]
Hypertension	110/188 (58.5%)	33/40 (82.5%)	16/19 (84.2%)	**0.003**[a,c]
History of smoking	94/179 (52.5%)	24/40 (60.0%)	13/19 (68.4%)	0.33
Medications				
RAS inhibitor	63/177 (35.6%)	23/40 (57.5%)	12/19 (63.2%)	**0.005**[a,c]
Anti-aldosterone	3/177 (1.7%)	0/40 (0.0%)	0/19 (0.0%)	0.60
Anti-platelet (non-aspirin)	8/177 (4.5%)	5/40 (12.5%)	4/19 (21.1%)	**0.011**[a,c]
Aspirin	39/178 (21.9%)	18/40 (45.0%)	9/19 (47.4%)	**0.002**[a,c]
Beta blocker	51/177 (28.8%)	16/40 (40.0%)	12/19 (63.2%)	**0.007**[b,c]
Statin	52/178 (29.2%)	23/40 (57.5%)	13/19 (68.4%)	**< 0.001**[a,c]
Non-statin lipid-lowering drugs	4/177 (2.3%)	1/40 (2.5%)	0/19 (0.0%)	0.80
Metformin	17/177 (9.6%)	7/40 (17.5%)	4/19 (21.1%)	0.16
Insulin	11/177 (6.2%)	4/40 (10.0%)	2/19 (10.5%)	0.59
Non-insulin/metformin anti-diabetics	11/177 (6.2%)	4/40 (10.0%)	1/19 (5.3%)	0.67
Doses of ICB received	2 (1–4) [n = 140]	2 (1–4) [n = 28]	2 (1.8–3.2)[n = 16]	0.40
Days since first ICB dose to presentation	42 (24–96) [n = 179]	36 (24–64) [n = 39]	32 (24–60) [n = 19]	0.32
Days since last ICB dose to presentation	18 (9–23) [n = 186]	20 (11.2–25.0) [n = 38]	14 (8.5–17.0) [n = 19]	0.10

	No significant CAD [n = 202]	CAD without coronary intervention [n = 40]	CAD and coronary intervention [n = 19]	p-value
Admission symptoms				
Fatigue	57/202 (28.2%)	16/40 (40.0%)	9/19 (47.4%)	0.10
Chest pain	50/202 (24.8%)	8/40 (20.0%)	6/19 (31.6%)	0.62
Dyspnoea	100/202 (49.5%)	10/20 (50.0%)	11/19 (57.9%)	0.78
Syncope	17/202 (8.4%)	3/40 (7.5%)	1/19 (5.3%)	0.88
Admission electrocardiogram *				
ST-elevation	23/202 (11.4%)	2/40 (5.0%)	4/19 (21.1%)	0.18
ST-depression	5/202 (2.5%)	3/40 (7.5%)	1/19 (5.3%)	0.26
Admission echocardiography				
Regional wall motion abnormality	70/174 (40.2%)	13/35 (37.1%)	8/17 (47.0%)	0.79
Left ventricular ejection fraction (%)	49.0 (35.0–60.0) [n = 179]	54.0 (40.0–60.0) [n = 36]	50.0 (40.0–58.0) [n = 16]	0.69
Initial troponin (multiple of institution ULN)	36.7 (7.9–157) [n = 167]	27.1 (5.8–60.8) [n = 40]	65.8 (19.4–239) [n = 15]	0.11
Initial troponin (>ULN)	155/167 (91.6%)	37/40 (92.5%)	15/15 (100%)	0.50
Peak troponin (multiple of institution ULN)	67 (22–232) [n = 161]	37 (14–84) [n = 40]	296 (96–759) [n = 15]	**0.009**[b,c]
Peak troponin (>ULN)	151/161 (93.8%)	38//40 (95.0%)	15/15 (100%)	0.59
Initial CK (multiple of institution ULN)	2.69 (0.61–17.75) [n = 144]	2.84 (0.49–13.32) [n = 30]	10.65 (4.28–23.26) [n = 14]	0.14
Peak CK (multiple of institution ULN)	3.56 (0.73–15.49) [n = 144]	4.06 (0.61–14.18) [n = 29]	10.73 (6.02–25.0) [n = 14]	0.16
Days from admission to LHC	2 (1–4) [n = 169]	2 (1–5.8) [n = 38]	1 (1–6) [n = 18]	0.78
Confirmed myocarditis (histology or cMRI)	127/166 (76.5%)	29/37 (78.4%)	10/19 (52.3%)	0.65
Other irAE	140/182 (76.5%)	25/40 (62.5%)	13/19 (68.4%)	0.65
Hepatitis	43/202 (21.3%)	6/40 (15.0%)	4/19 (21.1%)	0.66
Myositis	68/202 (33.4%)	16/40 (40.0%)	8/19 (42.1%)	0.60
Myasthenia-gravis like syndrome	74/202 (36.6%)	17/40 (42.5%)	10/19 (52.6%)	0.34
In-hospital management				
Vasopressors or inotropes	47/190 (24.7%)	6/40 (15.0%)	9/18 (50.0%)	**0.017**[b,c]
Steroids given within first 24 h	92/144 (63.9%)	29/36 (80.5%)	7/16 (43.8%)	**0.029**[a,b]
Initial steroid dose (mg) **	500 (75–1000) [n = 168]	750 (124–1000) [n = 36]	160 (113–1000) [n = 17]	0.32
Life-threatening arrhythmias ***	54/202 (26.7%)	5/40 (12.5%)	4/19 (21.1%)	0.15
In-hospital mortality	39/202 (19.3%)	4/40 (10.0%)	9/19 (47.4%)	**0.003**[b,c]
90-day all-cause mortality	60/158 (38.0%)	13/31 (41.9%)	11/17 (64.7%)	0.10

	No significant CAD [n = 202]	CAD without coronary intervention [n = 40]	CAD and coronary intervention [n = 19]	p-value
90-day irAE-related death	31/156 (19.9%)	6/31 (19.4%)	9/17 (52.7%)	**0.007**[b,c]
90-day myocarditis-related death	25/156 (16.0%)	5/31 (16.1%)	9/17 (52.7%)	**0.001**[b,c]

Abbreviations: CAD: coronary artery disease; RAS: renin angiotensin system; ICB: Immune checkpoint blocker; ULN: upper limit of normal of institution's lab; CK: creatinine kinase; LHC: left heart catheterisation; cMRI: cardiac magnetic resonance imaging; irAE: immune related adverse event. Bold is used for significant value.

[*] Other ST-modifications may have appeared after admission.

[**] Steroid dose normalised to equivalent of IV methylprednisolone.

[***] Include asystole, pulseless electrical activity, sustained ventricular fibrillation, sustained ventricular tachycardia, torsade de pointes, and complete heart block.

Statistics: Results are provided as median with interquartile range (25%–75%) and number (%). Kruskal–Wallis tests for continuous variables and Chi-squared tests (or Fisher's tests) for categorical variables. For variables with an overall significant difference among three groups, pairwise Wilcoxon tests or Chi-squared tests without correction for multiple testing were conducted.

[a] Significance between No CAD versus CAD without revascularization groups.

[b] Significance between CAD without revascularization versus revascularization groups.

[c] Significance between No CAD versus revascularization groups.