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Association among myocardial injury and mortality in Influenza: A prospective cohort study

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ABSTRACT

Background: Myocardial injury (MINJ) is a well-recognized prognostic marker in different acute cardio-respiratory illnesses, nonetheless, its relevance in Influenza remains poorly defined. Our aim was to assess incidence, correlates, short and mid-term prognostic role of MINJ in Influenza.

Methods: Hospitalized patients (pts) with laboratory confirmed Influenza A or B underwent highly sensitive cardiac T Troponin (hs-cTnT) measurement at admission in four regional Swiss hospitals during the 2018–2019 epidemic. MINJ was defined as hs-cTnT >14 ng/L. Clinical, laboratory and outcome data were prospectively collected. The primary endpoint was mortality at 28 days while the composite of mortality, admission to intensive care unit (ICU) or need for mechanical ventilation at 28-days and mortality at 30-months were set as secondary endpoints.

Results: The presence of MINJ was assessed within 48 h from admission in 145 consecutive hospitalized pts, being evident in 94 (65.5%) pts and associated with older age, higher C-reactive protein levels, renal impairment or chronic obstructive pulmonary disease. At a 28-days follow-up, 7 deaths (4.8%) occurred, all in patients with MINJ at admission (log-rank $p = 0.048$). MINJ was strongly associated with occurrence of death, ICU admission or mechanical ventilation (OR 5.74, 95% CI 1.28–53.29; $p = 0.015$). After a median follow-up of 32.7 months (IQR 32.2–33.4), 15 (10.3%) deaths occurred, all among pts with MINJ at index hospitalization leading to a higher mortality at follow-up among patients with MINJ (log-rank $p = 0.003$).

Conclusions: MINJ is common in patients hospitalized for Influenza and is able to stratify the risk of short-term adverse events and mid-term mortality.

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, Coronavirus Disease-19; CRP, C-reactive protein; hs-cTnT, High Sensitivity Cardiac Troponin T; ICU, Intensive Care Unit; IQR, Interquartile Range; LVEF, Left Ventricular Ejection Fraction; MINJ, Myocardial Injury; pts, patients.

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1. Introduction

Seasonal Influenza epidemic is a major health problem causing worldwide 3 to 5 million cases of severe illness and 290,000 to 650,000 deaths annually [1]. Infections occur at all ages, with varying clinical presentations ranging from mild symptoms to rapid and fatal courses, the latter more frequent in elderly, comorbid, patients [2].

Clinical or laboratory parameters for the identification of patients at increased risk of adverse outcomes are needed to stratify prognosis and guide the decision making, accordingly.

Retrospective analyses suggested a role for the modified Sequential Organ Failure Assessment (SOFA) Score as a tool able to identify patients at higher risk of worse in-hospital outcomes [3]. Individual risk factors such as older age, atrial fibrillation, acute heart failure and dementia were as well associated with a higher risk of in-hospital mortality in Influenza patients [4].

The prognostic relevance of myocardial injury (MINJ), defined as elevated cardiac biomarkers, has been recognized in several critical clinical conditions other than acute coronary syndrome and heart failure such as sepsis, pulmonary embolism, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS) and Coronavirus disease (COVID-19) infection [5–12]. Nonetheless its clinical relevance and prognostic value in hospitalized patients with Influenza remains poorly defined. So far only few previous retrospective studies evaluated the prognostic relevance of MINJ [10,13–16], with only one report assessing MINJ according to a definition based on highly sensitive troponin assays. Furthermore, no study has assessed the prognostic relevance of increased highly sensitive cardiac troponin values evaluated shortly after admission nor reported on the prognostic role of MINJ beyond the hospitalization phase.

We therefore designed the current study to prospectively assess the short- and mid-term clinical implications of Influenza related MINJ among consecutive hospitalized patients with Influenza to verify whether presence of increased highly sensitive troponin values measured at admission is able to stratify short and mid-term prognosis.

2. Methods

2.1. Patient population, objectives and endpoints

We included all consecutive hospitalized patients with a clinical diagnosis compatible with Influenza and a positive reverse transcription polymerase chain reaction for Influenza A/B on a nasopharyngeal swab across the four regional teaching hospitals (Lugano, Bellinzona e Valli, Locarno and Mendrisio) of Ticino canton, in Switzerland, during the 2018–2019 seasonal Influenza epidemic (from December, 1st 2018 to March, 31st 2019). Exclusion criteria were: age $<$ 18 years old; acute coronary syndrome; Tako-Tsubo cardiomyopathy; end stage renal disease (glomerular filtration rate (GFR) $<$15 ml/min/1.73m^2); severe hypertension (systolic blood pressure $>$ 200 mmHg), tachyarrhythmias (HR $>$150 bpm) or anemia (hemoglobin $<$90 g/L); severe COPD in chronic steroid therapy; known heart failure (HF) with a left ventricular ejection fraction $<$50%; stroke; pulmonary embolism; severe sepsis; massive rhabdomyolysis (e.g. burns); neuromuscular disorders; HIV infection; current treatment with systemic steroids or immunosuppressant; chronic illness with life expectancy $<$12 months; inability to give consent.

The main objective was to assess frequency, short- (28-day) and mid-term (30-months) prognostic implications of Influenza related MINJ defined as elevated high-sensitive cardiac troponin T (hs-cTnT) measured within 48 h from admission. The secondary objective was to investigate the predictors of Influenza related MINJ.

The present cohort also served as a comparison in a recent study by our group assessing the comparative frequency and prognostic impact of MINJ in COVID-19 and Influenza. A preliminary account of the data presented in this study were included in a previously published report [9].

The primary endpoint of interest was all-cause death at 28-days. Two secondary endpoints were the composite of all-cause death at 28-days, admission to an intensive care unit (ICU) or need for mechanical ventilation and all-cause death at 30 months .

2.2. Definition of myocardial injury

Troponin measurements were obtained in all patients with Elecsys Troponin T high sensitivity assay (Roche, Basel, Switzerland) which employs an immunoassay sandwich technique through two monoclonal antibodies specifically directed against human cardiac T Troponin. Measurements were obtained at each site using exclusively the Elecsys assay and adopting shared laboratory protocols, measurement units, and cut-off value (upper reference limit for hs-cTnT $\leq$14 ng/L).

MINJ was defined as hs-cTnT level above the upper reference limit (99th percentile) for the normal population. The cut-off used to define presence of MINJ was hs-cTnT $>$14 ng/L.

2.3. Data collection

A pre-specified set of clinical and laboratory variables were identified and obtained in all enrolled patients. Data were collected from the electronic health records from the four hospitals. Variables collected included demographics, laboratory measurements and in hospital outcomes. Follow-up information was obtained by assessing vital status in each patient with phone calls or querying the institutional databases (AV and LB). The Cantonal Ethic Committee approved the present study and all patients signed an informed consent.

2.4. Statistical analysis

Median and interquartile range (IQR) for continuous variables and counts and percent for categorical variables were reported. The Mann Whitney *U* test and the Fisher exact test were used to compare patients with and without MINJ. Non-collinear, clinically meaningful covariates with $p < 0.2$ at univariate analysis were included in a logistic model generated to identify independent correlates of Influenza related MINJ.

Events at follow up were assessed after database lock on November, 7th 2021. The median follow-up and IQR were computed using the reverse Kaplan Meier method. Mortality rates in the categories of interest per 100-person time, together with their 95% confidence intervals (CI) were also estimated. Cumulative (event-free) survival for Influenza patients by hs-cTnT ($\leq$ or $>$ 14 ng/L) was plotted and compared with the log-rank test. Cox regression model were fitted.

Statistical analyses were performed with the Stata software (release 16, Statacorp, College Station, TX, USA). A 2-sided $p < 0.05$ was considered as statistically significant.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines checklist for data reporting. Number of non-missing values for each variable are shown.

Authors will share the dataset from which the results were derived upon written reasonable request to the corresponding author.

3. Results

3.1. Patient characteristics

A total of 145 consecutive hospitalized patients with laboratory-confirmed type A/B Influenza on nasopharyngeal swab test were enrolled. All swabs resulted positive for Influenza A virus infection while in one patient both Influenza A and B viruses were detected. MINJ at admission was detected in 94 (65.5%) patients. Appendix fig. 1 reports patient's study flow while Table 1 reports baseline characteristics of study groups stratified according to the presence of MINJ at admission. Normal ranges of laboratory values are provided in appendix table 1.

Table 1
Baseline clinical characteristics and laboratory values in hospitalized patients with Influenza by presence of myocardial injury.

		All patients $n = 145$		hs-cTnT ≤14 ng/L $n = 51$		hs-cTnT >14 ng/L $n = 94$	
	No. of obs.		No. of obs.		No. of obs.		*p*-value
Age, years†	145	76 (67–85)	51	69 (54–79)	94	81 (72–88)	<0.001
Male sex, n (%)	145	64 (44.1)	51	22 (43.1)	94	42 (44.7)	1.000
Hypertension, n (%)	145	93 (64.1)	51	25 (49.0)	94	68 (72.3)	0.007
Diabetes, n (%)	145	32 (22.0)	51	8 (15.7)	94	24 (25.5)	0.211
COPD, n (%)	145	28 (19.3)	51	5 (9.8)	94	23 (24)	0.046
CVD, n (%)	145	39 (26.9)	51	14 (27.4)	94	25 (26.6)	1.000
BMI > 30, n (%)	145	13 (8.9)	51	5 (9.8)	94	8 (8.5)	0.770
Smoking, n (%)	145	28 (19.3)	51	10 (19.6)	94	18 (19.1)	1.000
OSAS, n (%)	145	8 (5.5)	51	1 (1.9)	94	7 (7.4)	0.261
Dyslipidemia, n (%)	145	59 (40.6)	51	15 (29.4)	94	44 (46.8)	0.052
Family history of CVD, n (%)	145	6 (4.1)	51	3 (5.8)	94	3 (3.1)	0.425
LVEF<50%, n (%)	145	2 (1.3)	51	0 (0)	94	2 (2.1)	0.541
Previous cerebrovascular diseases, n (%)	145	16 (11.0)	51	1 (1.9)	94	15 (16)	0.011
Hs-cTnT, ng/L†	145	19 (9–43)	51	7 (5–10)	94	34 (20–57)	
Hemoglobin, g/L†	145	131(120–142)	51	135 (125–145)	94	128 (118–142)	0.027
Leucocytes, n*10^9/L†	131	6.7 (5.0–9.2)	44	5.8 (4.3–7.6)	87	7.1 (5.1–9.8)	0.025
Lymphocytes, n*10^9/L†	119	0.76 (0.48–1.14)	41	0.76 (0.55–1.09)	78	0.74 (0.46–1.14)	0.319
C reactive protein, mg/L†	145	34 (14–60)	51	25 (10–50)	94	40 (18–67)	0.019
Creatinine, μmol/L†	145	85 (68–110)	51	77 (64–94)	94	93 (74–123)	<0.001
LDH, U/L†	89	419 (353–487)	27	396 (344–443)	62	443 (356–507)	0.097
Lactate, mmol/L†	88	1.3 (0.9–1.8)	27	1.3 (0.9–1.8)	61	1.3 (0.9–1.6)	0.615
PaO_2, mmHg†	85	58 (49–76)	26	55 (50–64)	59	61 (48–84)	0.248
Sat O_2, %	88	91 (85–95)	27	91 (87–94)	61	91 (85–96)	0.778
Radiologically confirmed pneumonia, n (%)	145	19 (13.1)	51	2 (3.9)	94	17 (18.0)	0.018
ICU admission, n (%)	145	18 (12.4)	51	2 (3.9)	94	16 (17.0)	0.032
Mechanical ventilation, n (%)	145	4 (2.7)	51	0 (0)	94	4 (4.2)	0.298
Mechanical hemodynamic support, n (%)	145	1 (0.7)	51	0 (0)	94	1 (1.1)	1.000
Length of hospital stay, days†	145	7 (5–9)	51	7 (5–7)	94	8 (6–10)	0.001

†Continuous variables reported as median (IQR)

Patients with MINJ were older and had higher prevalence of hypertension, chronic obstructive pulmonary disease (not requiring chronic steroid therapy), previous cerebrovascular diseases, radiologically confirmed pneumonia and higher leucocytes, C-reactive protein (CRP) and creatinine levels.

A repeated troponin assay measurement was available in 74 (51.1%) patients confirming presence of MINJ in 63 (88.7%) out of 71 patients with hs-TnT >14 ng/L at baseline.

3.2. Clinical and laboratory correlates of myocardial injury

Age (OR 2.15 per 10 years increase, 95% CI 1.48–2.84; $p < 0.001$), COPD (OR 5.15, 95% CI 1.37–19.31; $p = 0.015$), CRP (OR 1.82 per log unit, 95% CI 1.16–2.87; $p = 0.023$) and creatinine (OR 3.14 per log unit, 95% CI 1.17–8.40; $p = 0.009$) were identified as independent clinical and laboratory parameters associated with MINJ (Appendix table 2).

3.3. In-hospital outcomes

The median length of hospitalization was 7 days (95% CI 5–9), being longer in patients with as compared to those without MINJ [median 8 days (IQR: 6–10) vs. median 7 days (IQR: 5–7), $p < 0.001$].

Risk of ICU admission was significantly higher in MINJ patients (OR 5.02, 95% CI 1.10–22.81). Four patients needed mechanical ventilatory support, all with MINJ at admission. Influenza related myocarditis was clinically suspected based on the clinical presentation and echocardiographic data in 3 patients (3.2%). One of these patients needed mechanical hemodynamic support for advanced cardiogenic shock.

At 28-day follow up, seven deaths occurred leading to an overall mortality rate of 4.8% (rate 1.2 per 100 patients per week, 95% CI 0.6–2.6). All fatal events occurred in patients with MINJ, leading to a 28-day mortality rate of 7.4% (rate 1.9 per 100 patients per week, 95% CI 0.9–4.1). Causes of death are provided in the supplementary appendix. Cumulative survival was plotted separately for hospitalized patients with and without MINJ showing a significant lower short-term survival in patients with baseline hs-cTnT >14 ng/L (log-rank test $p = 0.048$, Fig. 1).

The composite endpoint of death, ICU admission or mechanical ventilation at 28-days occurred in 20 patients (13.8%). Of them, 18 had MINJ while 2 had admission hs-cTnT values <14 ng/L. A significant association between MINJ at admission and occurrence of the combined endpoint was evident (OR 5.74, 95% CI 1.28–53.29; $p = 0.015$).

The presence of MINJ at admission was associated with increased risk of death, ICU admission or mechanical ventilation at 28 days while controlling for other clinical parameters (continuous variables dichotomized at median) such as age < 76 years (OR 6.59; 95% CI 1.39–63.54; $p = 0.011$) and CRP >34 mg/L (OR 5.19; 95% CI 1.14–48.53; $p = 0.027$). The independent role of MINJ was also confirmed while adjusting for active smoking (OR 6.09, 95% CI 1.33–57.50; $p = 0.013$) and leucocyte count >7 n*10^9/L (OR 7.91, 95% CI 1.10–348; $p = 0.034$), while it resulted marginally non-significant when adjusting for impaired renal function (OR 4.68; 95% CI 0.99–44.58; $p = 0.051$). Fig. 2 shows a Forest-Plot reporting the results of a head-to-head bivariable comparison between clinical parameters and MINJ at admission to test their association with the secondary composite of all-cause death, ICU admission or need for mechanical ventilation at 28-days.

3.4. Follow-up

No patient was lost-to-follow-up. At a median follow-up of 32.7 months (IQR 32.2–33.4) 8 additional fatal events, for a total of 15 deaths, occurred (mortality rate 4.1 per 100 person year; 95%CI 2.5–6.8). All deaths observed at follow-up occurred in patients with evidence of MINJ at index hospitalization leading to a mortality rate of 6.6 per 100 person year (95% CI 4.0–10.9). Cumulative survival was plotted separately for hospitalized patients with and without MINJ showing a significant higher mid-term mortality in patients with hs-cTnT >14 ng/L at index admission (log-rank test $p = 0.003$, Fig. 3).

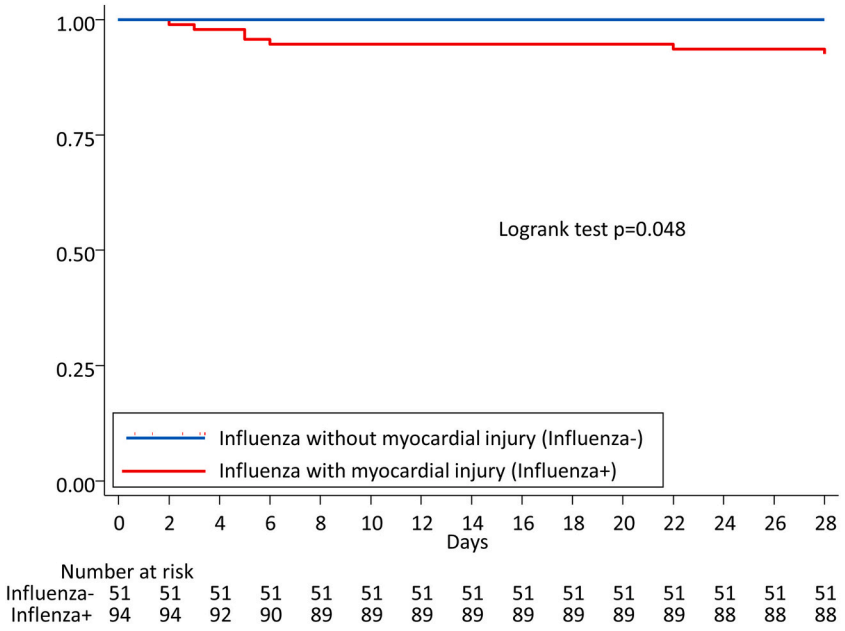

Fig. 1. Primary end-point: all cause death at 28-days. Cumulative survival curves for the primary endpoint of mortality at 28 days in hospitalized patients with Influenza stratified according to the presence of myocardial injury at admission.

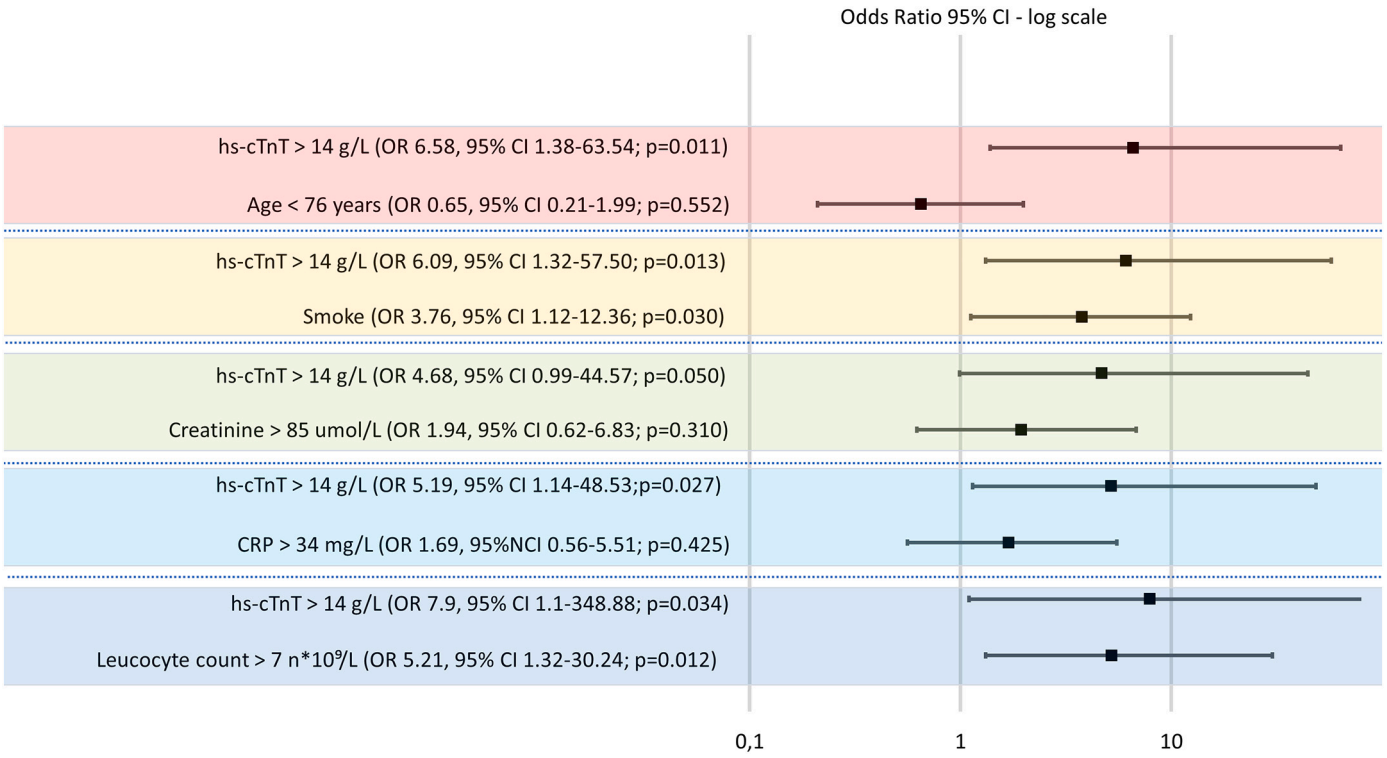

Fig. 2. Head-to-head bivariable comparison for the secondary composite endpoint at 28-days. Forrest-Plot reporting the results of the bivariable analysis to test the association of clinical and laboratory parameters against the presence of myocardial injury at admission for the secondary composite endpoint of mortality at 28 days, ICU admission or need for mechanical ventilation.

4. Discussion

The present study is the first, to the best of our knowledge, to prospectively investigate the role of MINJ among consecutive hospitalized patients with Influenza based on a highly sensitive troponin assay. Our main findings can be summarized as follows:

- MINJ assessed shortly after at admission is detected in 65.5% of patients hospitalized for Influenza and is independently associated with older age, higher CRP levels, renal impairment and COPD;
- MINJ identifies a patient subgroup at a higher likelihood of short and mid-term adverse events, including higher mortality, ICU admission, need for mechanical ventilation and death at follow-up.

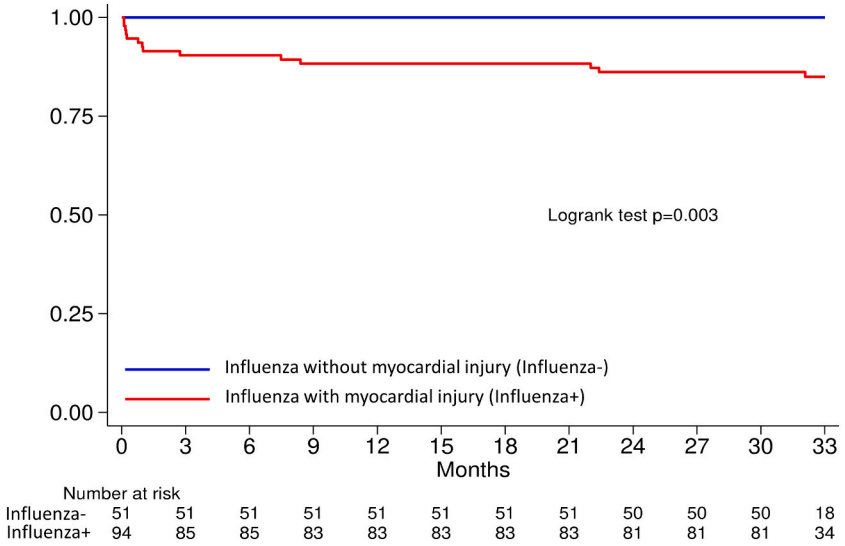

Fig. 3. Secondary endpoint: all-cause death at follow-up. Cumulative survival curves for the secondary endpoint of death at follow-up in hospitalized patients with Influenza stratified according to the presence of myocardial injury at admission.

There is emerging evidence on the role of MINJ in patients with different acute cardio-respiratory illnesses and COVID-19 [5–12,17–20]. As a contrary, there is limited data concerning the role of MINJ in patients hospitalized for Influenza with only few retrospective series published so far.

Ludwig et al. retrospectively analyzed 4469 veterans, with laboratory-confirmed Influenza enrolled during 2010–2012 epidemics, reporting MINJ in 25% when assessed by elevated non-highly sensitive Troponin I or Creatine Kinase-MB values [13]. Greaves et al., using an analogous definition, reported MINJ in 12% out of 152 hospitalized patients with laboratory-confirmed Influenza [14]. More recently, Harris et al. evaluated a retrospective cohort of 1131 patients hospitalized during 2017–2018 seasonal epidemic tested with low specificity troponin assays reporting MINJ only in 2.9% [15]. Currently, only a retrospective, single center, high-sensitivity troponin assay based study, reported incidence of MINJ in 31.8% of 264 patients with laboratory-confirmed Influenza [16], nonetheless no data are available on the temporal delay between hospitalization and sampling. None of the previously published retrospective analyses provided follow-up data.

Our study showed that Influenza associated MINJ, when evaluated shortly after admission with a high-sensitivity assay, can be detected in a much higher percentage of patients as compared with previous studies, being evident in in the 65.5% of our study group. Moreover, the value of hs-cTnT levels as prognostic marker for the identification of hospitalized Influenza patients at higher risk for adverse events carries potential relevant implications for practice. In our cohort, the presence of MINJ at admission identified patients at risk for short-term mortality and showed a significant association with the risk of death, ICU admission and mechanical ventilation, confirming and extending previous evidences. Indeed, while the relevance of hs-cTnT as prognostic marker in patients affected by different respiratory illnesses such as pneumonia, COPD, sepsis, ARDS and COVID-19 is more widespread acknowledged [5–12,17–20], only a single retrospective study suggested MINJ as marker of worse in-hospital outcomes in Influenza [16].

The association of MINJ with the composite endpoint of death, ICU admission or mechanical ventilation supports the value of hs-cTnT assessment in terms of morbidity and mortality risk stratification purposes beyond the impact of age, renal impairment and degree of inflammatory response as measured by CRP levels at bivariable analysis.

The relevance of some of these covariates has been recently confirmed in COVID-19 studies as age, cardiovascular disease, renal impairment, CRP levels and COPD have been linked to the occurrence of myocardial injury [19,20]. In line with previous findings, our analysis confirms the independent association of age, renal impairment, increased CRP and COPD.

A unifying mechanistic explanation linking the occurrence of MINJ and its associated prognostic impact in viral infections might be found in the peculiar endothelial tropism shared by Influenza and SARS-CoV2 viruses [21–24].

A central role of microvascular endothelial activation is known to be one of the pivotal pathogenic pathways in severe Influenza [23]. Endothelial activation also determines the expression of platelets-binding receptors with consequent platelet's adhesion, activation, formation of microvascular thrombi leading to vascular occlusion and ischemic damage [25,26]. All the above-mentioned mechanisms, while having acquired interest in COVID-19, have been also described in Influenza [27,28]. Dysregulation of this process creates the optimal milieu for the occurrence of thrombotic disorders causing further impairment of blood supply by vasoconstriction, inflammation and tissue edema, leading to organ damage, as seen in COVID-19 and Influenza related ARDS [28]. Those mechanisms clearly distinguish myocardial injury from inflammatory myocardial damage commonly seen in myocarditis. While the *primum movens* in Influenza and COVID-19 related myocardial injury appears to be a diffuse endothelial activation leading to microvascular thrombosis (with consequent modest increase in hs-cTnT), direct viral myocardial damage with evidence of viral replication is the responsible of (often significantly increased) hs-cTnT levels in myocarditis in cases. Thus, the immunothrombotic mechanism, should be thus considered as an adjunctive mechanism in work-up of patients with myocardial injury in the absence of obstructive coronary artery diseases, a mechanism so far neglected also from recent consensus documents [24,25].

Thus, also given the modest increase of hs-cTnT levels observed in our study (median value of 34 ng/L; 95% CI 20–57) and in line to different previous analyses [8,9,11,14,16,17–20], MINJ should not be interpreted as the ultimate determinant of outcomes, but rather as a marker of worse clinical severity with systemic involvement, the latter driving prognosis.

Presence of MINJ in patients admitted to the emergency department is a common finding as evidenced by the prospective UTROPIA study which enrolled 1640 patients showing that about 1 out of 4 patients had baseline hs-cTnI levels above the 99th percentile [29]. In addition, Chapman et al., reported in a prospectively enrolled cohort of patients with myocardial injury a strikingly high 5-year mortality of 72.4%,

mainly driven by non-cardiovascular events [30]. Also in our series, short and mid-term mortality were driven by non-cardiovascular events, with acute respiratory failure being the leading cause of death (additional details provided within the supplementary appendix).

Thus, while our data extend previous evidence on the deleterious impact of MINJ also to patients hospitalized for Influenza, it remains unclear whether MINJ per se, or the presence of multiple associated comorbidities leading to a greater likelihood of MINJ, are the true determinants of worse mid-term outcomes. Nonetheless, the clinical significance of hs-cTnT measurement at admission in influenza as well as in other respiratory and inflammatory conditions such as COVID-19, COPD, and sepsis remains.

Independently from mechanisms behind MINJ, assessment of hs-cTnT values at admission might represent a fast, easy to obtain, widely available marker that could spot, shortly after admission, among hospitalized Influenza patients those at high risk for short term adverse events and thus guide the decision-making process.

4.1. Limitations

Several limitations of this study should be considered when interpreting our findings. First, our study was exploratory in nature and not based on a formal sample size calculation or minimum number of primary events to be accrued. As a consequence, the low number of primary events hindered the possibility to assess predictors of in-hospital mortality by multivariable regression analyses.

While hs-cTnT measurement was mandated per protocol at admission, decision on serial measurements was left to the caring physician, thus no serial testing is available.

The explorative nature of our analysis did not allow a systematic use of ECG as well as cardiac imaging, except for those rare cases with clinically suspected Influenza-related myocarditis, nonetheless nor MRI neither endomyocardial biopsy were routinely performed in those cases. Finally, cohorts of patients with and without MINJ at admission differ significantly for relevant baseline clinical characteristics, which could not correct at multivariable analysis. Additionally, while in presence of a comparator represented by patients with negative troponin assessment at admission, lack of a control group with comparable baseline characteristics represents a further significant limitation of our approach. For these reasons, no causative relationship can be drawn between presence of MINJ and outcomes, but our findings should be considered hypothesis generating.

In conclusion, Influenza-related MINJ, evaluated with high sensitivity cardiac Troponin assays is frequent among hospitalized patients and has shown to be associated with a high likelihood of short and mid-term adverse events. Increased hs-cTnT levels represents an easy to use, widely available marker able to identify patients at increased risk of adverse outcomes and to stratify prognosis. Our data extend to Influenza the concept of viral infections as primary endothelial diseases, with myocardial injury being one of its measurable consequences and stress the pivotal role of the cardiovascular system in systemic acute viral illnesses.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.08.016.

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