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Original Research Article

An Evaluation of the Appropriateness of Prescribing Ultrasensitive Cardiac Troponin I in the Emergency Department of the Mohammed V Military Training Hospital in Rabat

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Abstract: In emergency medicine, Troponin Ic is a useful diagnostic and prognostic biomarker in the management of ischemic cardiac pathologies. However, its prescription often exceeds international recommendations. The aim of this study is to evaluate practices concerning the prescription of Troponin assays in the emergency department of the Mohammed V Military Training Hospital in Rabat. This is a prospective study. Was included in this study, every patient admitted to the emergency department of the Mohammed V Military Training Hospital in Rabat and having at least one troponin assay during the period from December 25, 2020 to January 12, 2021. The assay was performed using the "ARCHITECT STAT Highly sensitive troponin-I" method. 135 patients for whom have prescribed a Troponin assay during the period of study. A total of 219 assays were performed. The mean age was 64 years, with a predominance of males. The main reasons for admission were chest pain (29.6%), dyspnea (26.6%), neurological disorders (16.3%) and respiratory distress (10.3%). A high Troponin Ic value during the first determination was observed in almost 37% of cases. In 63% of cases, the value was negative. 53.3% of prescriptions were considered as irrelevant according to pre-established criteria. A repeated Troponin Ic assays were performed in 31% (n=127) of cases. They were deemed relevant in 25% of cases. In 6% of patients, the appropriateness of repeat assays was not demonstrated. Compliance with good prescribing practices for Troponin significantly reduces the number of unjustified samples, with a real economic impact.

Keywords: Clinical Relevance, Biolpogical Assay, Troponin Ic, Emergency department, prescription, ischemia.

INTRODUCTION

Troponin is a protein complex consisting of three subunits: T (TnT), I (TnI) and C (TnC), involved in the regulation of striated muscle contractions. The value of assaying the cardiac isoform of troponin I lies in its near-absolute specificity for myocardial tissue and its high sensitivity, enabling the detection of very small areas of necrosis. (Viallon. A *et al*., 2006), (Christenson. E *et al*., 2013). The development of specific antibodies for this cardiac isoform has made precise measurement of this protein possible (Godet. G *et al*., 2009), (Lavoinne. A *et al*., 2004).

The prescription of troponin Ic in emergency departments is particularly relevant for the diagnosis and stratification of ischemic risk, especially in patients admitted for non-ST-segment-shift myocardial infarction (Godet. G *et al*., 2009), (Pruvot. S *et al*., 2006), (Batard. E *et al*., 2004). Currently, this biomarker plays a role in the prognostic assessment of patients with SARS-CoV-2 infection, with TnIc values significantly increased in patients with severe infection compared with those with milder forms of the disease (Lippi. G *et al*., 2020).

While the contribution of this marker in emergency situations is undeniable, its over-prescription can lead to inappropriate admissions to the Cardiac Intensive Care Unit (CICU) or to the performance of unjustified coronary angiographies, with a non-negligible economic impact and induced iatrogenicity (Florian. G, 2015). In our training program, we observed an increase in the number of requests for cardiac troponin

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assays during admission to the emergency department. This prompted us to question the relevance of this prescription. We therefore conducted a study in the emergency department (SAU) of the Mohammed V Military Training Hospital in Rabat (HMIMV), in close collaboration with medical and paramedical staff.

The main aim of this study is to detect anomalies and optimize the use of this biomarker, thus contributing to the improvement of professional practices in a spirit of mutual collaboration.

MATERIALS AND METHODS

This is a prospective descriptive study. Any patient aged over 15 years, admitted to the emergency department of the the Mohammed V Military Training Hospital (HMIMV) in Rabat and having at least one Troponin assay during the period from December 25, 2020 to January 12, 2021. Troponin assays performed in pediatric and Gynecological and Obstetric Emergencie were excluded, as were patients with incomplete medical records.

Survey data were collected using a data collection form filled in from each patient's medical record, available on the hospital's information systems. The study database was transcribed into a Microsoft EXCEL® table, including: date of admission to the emergency department (ED), age, sex, reason and outcomes of admission, personal history, cardiovascular risk factors, electrocardiogram (ECG) results, troponin assay results, diagnosis, patient referral and whether the patient had been infected with SARS-CoV2.

Samples were collected in a heparinized plasma tube for troponin determination, and transported to the HMIMV Biochemistry and Toxicology Laboratory, which uses the microparticle chemiluminescence immunoassay (CMIA) technique for the quantitative determination of cardiac troponin I (TnIc) in human serum and plasma on the ARCHITECT i system Abbott HS® [9].

Troponin was considered positive at over 15.6 ng/l in women and over 34.2 ng/l in men [9]. Data analysis was performed using Jamovi version 2.4 software. Quantitative variables were expressed as mean +/- SD or medians, depending on their distribution. For qualitative variables, data were presented as numbers and percentages, and were compared using the chi-square test or Fisher's exact test. The p-value was considered statistically significant when it was < 0.05.

RESULTS

Of 204 patients, only135 were included; the remaining 69 were excluded because of incomplete medical records. The mean age was 64±14 years, with extremes ranging from 25 to 91 years. Males predominated, with a sex ratio of 2.1. 49.6% of patients (n = 67) had cardiovascular risk factors, mainly diabetes in 31% (n = 42), hypertension in 28.9% (n = 39) and smoking in 17.7% (n = 24), 25.9% of patients (n=35) had a history of heart disease. 8.1% of patients (n = 11) had a history of COVID-19.

Chest pain was reported in 40 patients (29.6%), dyspnea in 36 (26.6%), neurological disorders in 22 (16.3%), respiratory distress in 14 (10.3%), epigastric pain in 9 (6.6%), influenza-like illness in 8 (5.9%), anemia in 8 (5.9%), and altered general condition in 7 (5.1%).

The 135 patients included in our study underwent at least one TnIc assay. Table 1 shows the distribution of TnIc assay relevance according to assay frequency, with a total of 219 TnIc assays performed.

Table 1: Distribution of the relevance of TnIc assays according to assay frequency

	Frequency of TnIc determinations							**p-value**
Relevance of assays	1	2	3	4	5	6	Total	
Relevant N (%)	71 (98.6)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	72 (100)	< 0.001
Irrelevant n (%)	22 (34.9)	18 (28.6)	10 (15.9)	8 (12.7)	3 (4.8)	2 (3.2)	63 (100)	
Total n (%)	93 (68.9)	19 (14.1)	10 (7.4)	8 (5.9)	3 (2.2)	2 (1.5)	135(100)	

A high TnIc value (positive TnIc) on initial assay was observed in almost 37% of the sample population (n=50/135). In 63% of cases (n=85/135), the level of this marker was within the range of reference values provided by the manufacturer (negative TnIc) (p= 0.003).

Analysis of the patient records included in this study shows that only 46.7% (n=63) of initial TnIc prescriptions were deemed relevant according to international recommendations. Repeat TnIc determinations were performed in 42 patients. (n=42/135). This represents 127 samples. They were deemed relevant in 34 patients (25% of cases), all of whom received two or more TnIc assays. In 5 patients (5/34), these tests were used to check an initial negative assay, and in 29 patients (29/34), they were requested as part of the follow-up to an initial positive TnIc. In the remaining 8 patients (6%), the relevance of repeated assays was not demonstrated. In fact, TnIc was

sometimes prescribed three or even four times for the same patient without justification (figure 1).

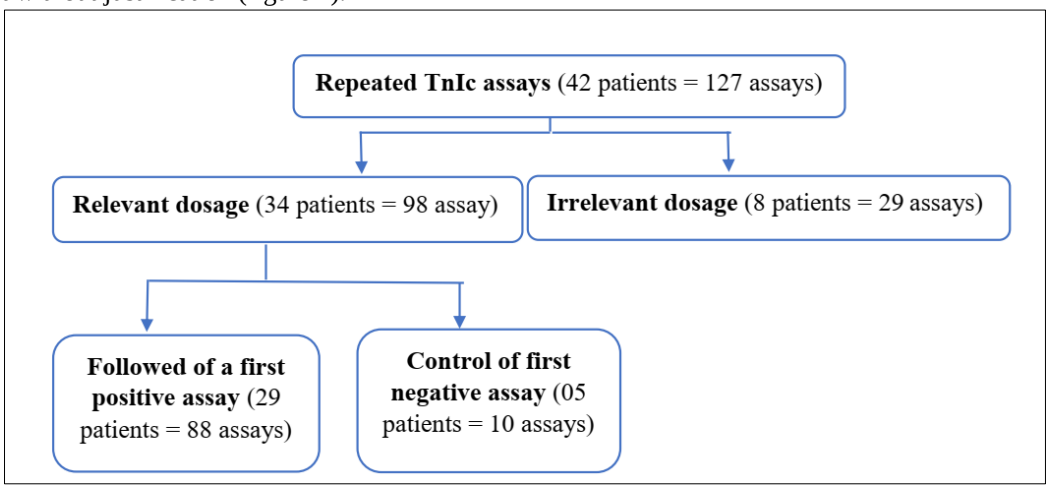

Figure 1: Analysis of the relevance of multiple assays

The reason and outcomes of admission in our population are shown in Figure 2.

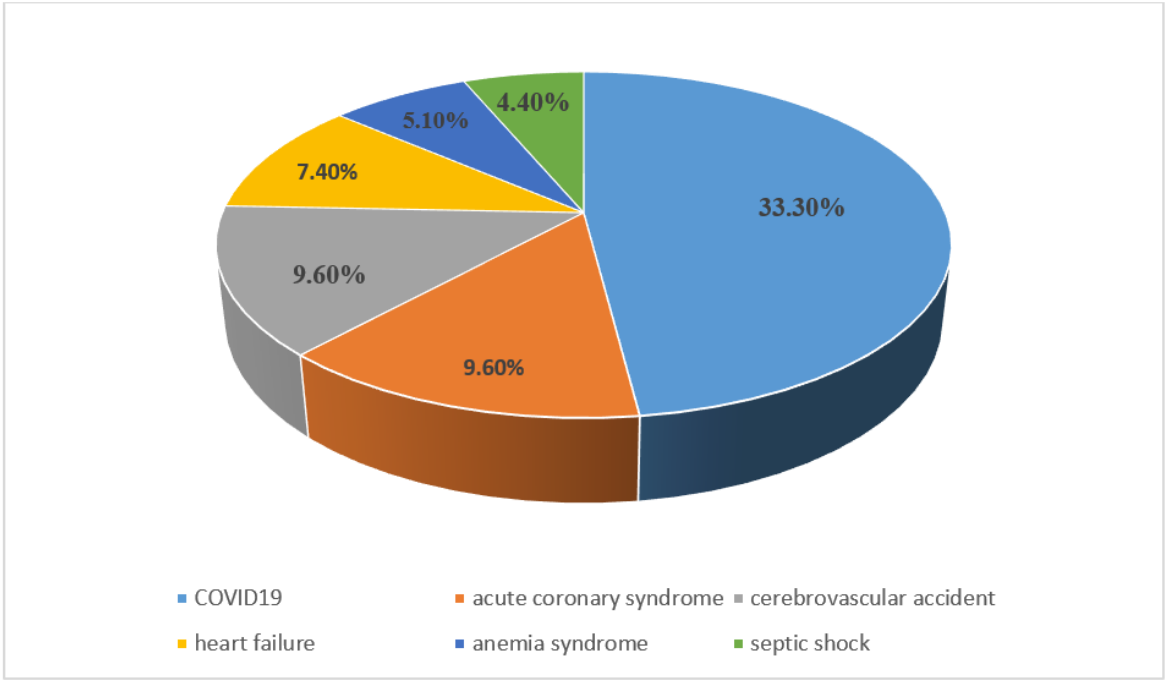

Figure 2: Main diagnoses in our population

DISCUSSION

Troponins are essential structural proteins of the myocyte contractile system, regulating muscle activity in response to intracellular calcium. There are three isoforms, T, C and I, of which the Ic isoform is cardiospecific (Florian. G, 2015). According to the Euro-North American consensus, the measurement of troponin Ic plays a crucial role in differentiating between two types of non-ST+ acute coronary syndromes: non-ST infarcts, characterized by elevated troponin, and unstable angina, marked by the absence of elevated troponin (Antman. E *et al.*, 2000). On the other hand, in the absence of clinical manifestations of ischemia, an increase in troponin should prompt a search for another cause. There are a number of possible causes, including myocarditis, pulmonary embolism, severe heart failure, septic shock, use of cardiotoxic drugs, respiratory failure, cirrhosis, digestive hemorrhage, metastases and end-stage renal failure. This explains why the determination of this parameter is not pathognomonic of ischemic pathology (Barasch. E *et al.*, 2000). Moreover, this biomarker plays a crucial role in the prognostic evaluation of patients with SARS-CoV-2 infection (Lippi. G *et al*., 2020).

There are currently numerous methods for determining plasma TnIc, based on antibodies recognizing different epitopes and leading to specific standards for each kit (BIRCAN.C.M, 2010).

There is a threshold value for each troponin. With troponin I, however, the situation is more complex. This is due, on the one hand, to the fact that there is no standard preparation for troponin I, so each laboratory prepares its own troponin sample for calibration (Christenson. RH *et al*., 2001); and, on the other hand, to the fact that each laboratory's antibodies bind to different troponin epitopes. To compensate for this heterogeneity, the IFCC (International Federation of Clinical Chemistry) has proposed the introduction of two decision thresholds for troponin in order to standardize markers of myocardial distress:

- A low threshold corresponding to the 99th percentile of a population of healthy volunteers, with an analytical coefficient of variation of less than 10%. Values above this 99th percentile suggest the existence of myocardial damage.
- Higher threshold corresponds to the best specificity-sensitivity compromise for the diagnosis of acute coronary syndrome (ACS) (Panteghini. M *et al*., 2004).

Assays considered "ultra-sensitive" are characterized analytically by very low 99th percentile values and an analytical precision of 10% for values close to, or even below, the 99th percentile. Their adoption has had a number of consequences, including improved analytical reliability for low values and a reduction in 99th percentile values, which are now close to ten µg/L (Melanson. SE *et al*., 2007). As a result, it is now possible to detect more frequently small variations in troponin that were not quantified by the first generations of these assays.

However, the interpretation of ultrasensitive troponins is not unequivocal. For example, their slight variations could be explained by "physiological" variations in troponin, linked to age or sex, with values appearing to be higher in older subjects, and for the same age group, higher in men than in women. These variations could also relate to pathologies of extracardiac origin leading to myocardial suffering (Melanson. SE *et al*., 2008).

According to the latest ESC 2020 recommendations on the management of ST-ACS, diagnosis is based on four elements: clinical presentation, ECG, initial troponin value (H0) and troponin variations (Guedeney. P *et al*., 2021).

It is recommended that cardiac troponin be measured by ultrasensitive assays and that results be reported within 60 minutes.

The European Society of Cardiology (ESC) 0H/1 H algorithm is the reference algorithm (figure 3) for the diagnosis of ST- ACS, whenever the necessary assay is available in the center.

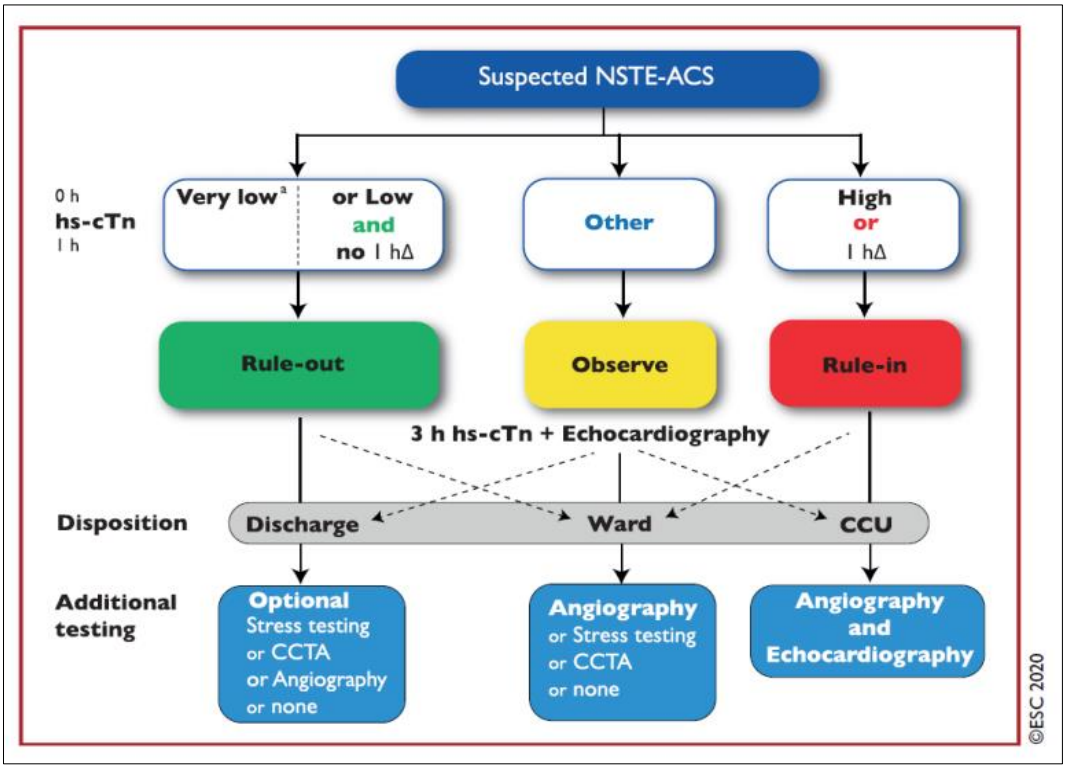

Figure 3: 0 H/1 H exclusion and inclusion algorithm using high-sensitivity cardiac troponin assays in hemodynamically stable patients with non-ST-segment elevation acute coronary syndrome in the emergency department. This algorithm is used if the patient presents beyond H3 (Guedeney. P *et al*., 2021)

An assay at H3 is recommended if both 0 H and 1 H values are inconclusive and the clinical presentation is strongly suggestive of ACS.

As an alternative to the ESC 0 H/1 H algorithm, it is recommended to use the ESC 0 H/2 H algorithm with blood sampling at 0 H and 2 H, if an ultrasensitive troponins assay with a validated 0 H/2 H algorithm is available (figure 3) (Guedeney. P *et al*., 2021).

Patients in the yellow zone represent 25% of the population and require a 2nd troponin assay. In 75% of cases, a single assay is sufficient to make the diagnosis (Guedeney. P *et al*., 2021).

Our study shows a male predominance, which is in line with the data in the literature. In two studies, one from France and the other from Morocco (Lachery. C, 2016), (Kabbaj. H *et al*., 2018), coronary pathology affects the male population in two-thirds of cases (Akoudad. H *et al*., 2004). In women, it is rare in the pre-menopausal period, in the absence of other risk factors. After the menopause, the risk increases and reaches that of men.

The average age found in our study (64 years) is similar to the study reported by (Kabbaj. H *et al*., 2018) (63 years) and LACHRY (61.5 years) (Lachery. C, 2016). Age is a major risk factor for cardiovascular disease (De Gevigney. G *et al*., 2003). At cardiac level, the myocardium also ages with age, and ventricular rhythm disorders become more frequent, with loss of vessel elasticity and β-adrenergic receptor sideration leading to a reduction in regulatory systems. Coronary and aortic calcifications also increase with age.

In our study, 49.6% of patients had cardiovascular risk factors, consisting essentially of: diabetes in 31% of cases, hypertension in 28.9% of cases, and heart disease in 26% of cases. This result is comparable to that found in the study by (Lachery. C, 2016) on a population of 186 cases, who reported: hypertension in 42% of cases, diabetes in 13% and heart disease in 22.9% of patients.

The usefulness of troponin assay should be assessed primarily in the first few hours of management of chest pain (Hammerer-Lercher. A *et al*., 2001) and symptoms suggestive of acute coronary pathology after ECG is performed within 10 minutes of admission to the ED, as recommended by ESC 2020 (Guedeney. P *et al*., 2021). Thus, based on the results of our analysis, it would appear that its prescription in emergency departments for chest pain is strictly in line with cardiological recommendations (Roffi. M *et al*., 2016).

As for patients with dyspnea (n=36), TnIc came back positive in 13 of them, although the diagnosis of ACS was retained in only 2 cases. These results illustrate the potential difficulty of interpreting TnIc in patients with dyspnea. Indeed, if the dyspnea is related to left heart failure or pulmonary embolism, a low elevation of this marker may be observed, and is not necessarily related to ACS (Wurtz. E *et al*., 2008). In addition to the clinical situations described above, it is important to note that 14 patients in our population (10.3% of cases), whose reason for consultation was respiratory distress, also benefited from an emergency troponin assay. This finding has not been reported in other similar studies conducted in recent years, and could be explained by the occurrence of the global corona virus disease 2019 pandemic (COVID19) during the period of our study, the virus responsible for which is thought to cause increased cardiovascular risk in infected patients (El Boussadani1. B *et al*., 2020).

In the present study, the majority of our patients received a single troponin assay (68.9%, n=93/135), which is in line with the results of the OUMMADA study (Oummada. A, 2010), in which 90.9% of cases received a single assay. Concerning multiple assays, 31% of our population benefited from a cycle compared with only 9.1% of the population in the OUMMADA study (Oummada. A, 2010).

A negative result does not rule out cardiac pathology, especially if the delay between the onset of pain and treatment is < 4 hours. The results of the second assay are used to confirm the absence of cardiac pathology in the case of a negative result, or to conclude that cardiac pathology is present in the case of a positive result (Guillaume. L *et al*., 2009).

Our study shows that the troponin assay method recommended in figure 3 was followed by the prescriber in cases of strong suspicion of ACS. In our population, multiple assays are carried out either to check an initial negative assay, or as part of the follow-up of patients with a confirmed diagnosis of ACS, or in the event of other myocardial pathology.

Of the 135 initial TnIc assays performed in our study, only 37% (n=50) were positive. Table 2 compares the results of various studies (Kabbaj. H *et al*., 2018), (Oummada. A, 2010), with our own.

Table 2: Results of initial TnIc assays in different studies compared to our study

	Our study 2020/2021	**KABBAJ. H *et al*., 2018**	**OUMMADA.A, 2010**
Number of cases	135	71	410
Positive TnIc assay (1st determination)	37%	26%	24,6%

In our study, 46.7% (n=63) of TnIc assay prescriptions were deemed relevant in accordance with international recommendations, compared with 68.3% (n=127/186) reported by LACHERY's study (Lachery. C, 2016). This means that in over 53.3% of cases in our population, the assay did not comply with these recommendations. From these results, we can see that the request for TnIc assay is less relevant in our study than in LACHERY's study. This may be explained by the prescribers' fear of missing a vital emergency.

31% (n=42/135) of our patients benefited from repeat assays. The prescription of troponin cycles was deemed appropriate in 25% (n=34/135) of cases, the majority of which (n=29/34) were performed as part of a follow-up. However, examination of the files shows that some patients, representing 6% of cases (n=8/42), received 3 or even 4 doses, without justification.

Table 3: Compares our results with those of other studies (Lachery. C, 2016), (Oummada. A, 2010)

	Our study 2020/2021	**LACHERY.C *et al*., 2016**	**OUMMADA.A, 2010**
Number of cases	135	186	410
Troponin cycles	31%	14.5%	9.02%
Justified cycles	25%	/	5.1%
Unjustified cycles	6%	/	3.92%

This comparison shows that our population benefited from a greater number of troponin cycles than other studies (Lachery. C, 2016), (Oummada. A, 2010).

Among the 135 patients identified, the reason and outcomes of admission were, in order of frequency: SARS-Cov 2 infection in 45 patients (33.3%); Acute coronary syndrome in 13 patients (9.6%); cerebrovascular accident (CVA) in 13 patients (9.6%); heart failure in 7.4% (10 patients); anemia syndrome in 5.1% (7 patients) and septic shock in 4.4%. 30.3% of patients were classified in the "other pathologies" group. These results are similar to those reported by French BIRCAN study (BIRCAN.C.M, 2010). Table 4

Table 4: The main diagnoses in our population and their comparison with the results of another study

	Our study 2020/2021	**BIRCAN.C.M 2010 (12)**
Number of cases	135	5694
COVID19	33.3%	-
Acute coronary syndrome	9,6%	5.5%
Cerebrovascular accident	9.6%	2.6%
Heart Failure	7.4%	-
Septic Shock	4,4%	0.7%
Other	30,3%	63%

Our results show that one-third of our population was diagnosed as infected with the SARS-Cov-2 virus. This finding, unprecedented in our series compared with previous work, can be explained by the fact that our study was carried out at the height of the global Covid-19 pandemic, whose suspected cases, managed strictly in hospitals during our study period, were the main patients admitted to emergency departments.

CONCLUSIONS

Troponin measurement is frequently requested in the emergency department, given its value in the diagnosis and management of acute coronary syndrome. However, under no circumstances should it become a routine test. Moreover, the economic impact of unjustified TnIc determinations is far from negligible. Our evaluation of troponin assay prescription practices in the emergency department of the HMIMV in Rabat showed that 53.3% of troponin assay requests were outside the guidelines (ESC2020). The majority of irrelevant prescriptions in our study were probably made as part of a search for cardiac damage secondary to SARS-Cov2 infection, especially in patients with cardiovascular comorbidities, according to recent studies showing the direct impact of this virus on the cardiovascular system (El Boussadani1. B *et al*., 2020). Adherence to good troponin prescription practices will significantly reduce the number of unjustified and medically useless samples, with a real economic impact.

Conflicts of Interest: The authors declare no conflict of interest.

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