European Review for Medical and Pharmacological Sciences 2022; 26: 1777-1785

Predictors of in-hospital mortality of COVID-19 patients and the role of telemetry in an internal medicine ward during the third phase of the pandemic

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Abstract. – OBJECTIVE: The first pandemic phase of COVID-19 in Italy was characterized by high in-hospital mortality ranging from 23% to 38%. During the third pandemic phase there has been an improvement in the management and treatment of COVID-19, so mortality and predictors may have changed. A prospective study was planned to identify predictors of mortality during the third pandemic phase.

PATIENTS AND METHODS: From 15 December 2020 to 15 May 2021, 208 patients were hospitalized (median age: 64 years; males: 58.6%); 83% had a median of 2 (IQR,1-4) comorbidities; pneumonia was present in 89.8%. Patients were monitored remotely for respiratory function and ECG trace for 24 hours/day. Management and treatment were done following the timing and dosage recommended by international guidelines.

RESULTS: 79.2% of patients necessitated O_2-therapy. ARDS was present in 46.1% of patients and 45.4% received non-invasive ventilation and 11.1% required ICU treatment. 38% developed arrhythmias which were identified early by telemetry and promptly treated. The in-hospital mortality rate was 10%. At multivariate analysis independent predictors of mortality were: older age (R-R for≥70 years: 5.44), number of comorbidities ≥3 (R-R 2.72), eGFR ≤60 ml/min (RR 2.91), high d-Dimer (R-R for≥1,000 ng/ml:7.53), and low PaO_2/FiO_2 (R-R for <200: 3.21).

CONCLUSIONS: Management and treatment adherence to recommendations, use of telemetry, and no overcrowding appear to reduce mortality. Advanced age, number of comorbidities, severe renal failure, high d-Dimer and low P/F remain predictors of poor outcome. The data help to identify current high-risk COVID-19 patients in whom management has yet to be optimized, who require the greatest therapeutic effort, and subjects in whom vaccination is mandatory.

Key Words:
SARS-CoV-2, Respiratory insufficiency, ARDS, Arrhythmia, Comorbidity.

Introduction

COVID-19 continues to be an emergency/urgency around the world despite the fact that we have vaccines today. Numerous studies have evaluated the predictive risk factors for in-hospital mortality of patients with COVID-19 during the first pandemic phase that was characterized by high in-hospital mortality, ranging from 23% to 38%[1-9]. Most of the studies were retrospective, multicenter with many cross-sectional variables. In addition, therapeutic approaches and the ability to care for critically ill patients have been reduced. Therefore, the above conditions may have influenced the results of the analyzes. The second pandemic phase and, in particular, the third pandemic phase of COVID-19 was characterized by

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an overall improved management approach based on greater clinical experience that likely led to an improvement in the outcome of the disease. Today, even if we do not have a cure, there are many pharmacological supports, e.g., antivirals, corticosteroids, heparin, monoclonal antibodies, etc., which could improve the prognosis if used at the right timing and in selected patients[10,11]. In addition, there has been an improvement in the management of respiratory failure, with better use of non-invasive and invasive respiratory assistance, and of complications of SARS-CoV-2 infection, e.g., coagulopathy. Arrhythmias are known to occur in COVID-19, highlighting the need to monitor cardiac function to limit or prevent the risk of fatal arrhythmias[12]. Therefore, in light of the profound changes in the management of COVID patients in the third pandemic phase, it is important to identify patients at greatest risk of poor prognosis upon admission to hospital. This can ensure that they receive the utmost attention in their timely handling and treatment. Also, it could be useful to identify individuals in the general population who should receive the most attention in infection prevention practices.

Accordingly, we planned a prospective study with the aim to evaluate the factors, at hospitalization, predicting in-hospital mortality of COVID-19 patients during the third pandemic phase.

Patients and Methods

All COVID-19 patients admitted consecutively from 15 December 2020 to 15 May 2021 at the Internal Medicine COVID-19 CENTER of the Vanvitelli University Hospital were included in the study. In our COVID-19 CENTER there was no overcrowding or overwhelming since the number of beds was fixed and the number of hospitalized corresponded to the number of pre-established beds and all patients were monitored remotely for all vital functions 24 hours a day.

The presence of SARS-CoV-2 was assessed by nasal/throat swabs by RT-PCR. An anamnestic form was compiled for all patients about their previous and active diseases, pharmacological treatments and the time of symptoms onset referable to SARS-CoV-2 infection. At the time of admission, all patients underwent a chest CT scan and the lung injury was assessed by a score of 0-20. In addition, the patients underwent an ultrasound examination of the chest that quantified lung injury using a (LUS) score of 0-36. A blood gas analysis (EGA) was performed in all patients and the PO_2/FiO_2 ratio was estimated. Hematological and renal functions were evaluated by performing the following laboratory analyses: red and white cells and platelet blood count, hemoglobin, serum creatinine, blood urea, estimated glomerular filtration rate (eGFR); liver function by detecting AST, ALT, bilirubin, albumin, gamma-globulin. Respiratory function was remotely monitored 24 hours/day, cardiovascular functions were monitored by cardiac telemetry (Dräger Vista 120 S, Drägerwerk AG, Lübeck, Germany) for 24-hour/day, and echocardiography, when required.

Patients were treated according to the severity of hypoxemia using O_2-therapy by nasal cannula, Venturi mask, high flow nasal cannula or non-invasive ventilation (NIV). Drug therapy with antiviral (remdesivir), dexamethasone, low molecular weight heparin and tocilizumab was given following the timing and dosage recommended by international institutions and proposed by Italian Drug Agency (AIFA)[11]. In particular, only patients with symptoms onset within 10 days and who required oxygen therapy were candidate to antiviral treatment with remdesivir, administered at dosage of 200 mg the first day (followed by) and then 100 mg/daily for 4 days. Dexamethasone was given to patients who required O_2-therapy or NIV, at a dosage of 6 mg/daily for 10 days. All patients received prophylactic low molecular weight heparin or therapeutic dosage, when necessary. Specific antibiotic therapy was given when bacterial infection was detected or empirical one when strongly suspected. All active concomitant diseases were treated according to respective guidelines. The study was conducted in accordance with the Principles of Good Clinical Practice Guidelines and all patients signed informed consent. The study was approved by the Local Ethics Committee of the University of Campania Luigi Vanvitelli, Naples, Italy.

Statistical Analysis

Results are expressed as median and interquartile range (IQR). The Mann-Whitney U test was used to evaluate differences between death and alive groups. The chi-square test with Yates correction was used to evaluate difference between categorical variable of the two groups. The variables present at hospital admission and included in the analysis were: age, sex, overweight/obesity, smoking, d-Dimer, fibrinogen, CRP, ferritin, renal failure, hypertension, diabetes, COPD, PaO_2/fiO_2 ratio, CT score, LUS score,

Table I. Baseline demographic and clinical characteristics of the 208 COVID-19 patients admitted to our COVID-19 Center.

Characterists at baseline	Value
Number of patients	208
Age, yrs, median (IQR)	63 (53-73)
Male, n (%)	123 (59.4)
Smoke (present or past), n (%)	98 (47.1)
Overweight/Obesity, n (%)	77(37)
Type 2 diabetes, n (%)	52 (25)
Hypertension, n (%)	116 (55.8)
Chronic kidney failure, n (%)	76 (36.5)
Chronic liver disease, n (%)	24 (11.5)
COPD, n (%)	31 (14.9)
Chronic vasculopathy, n (%)	41 (19.7)
Active cancer, n (%)	8 (3.8)
N° of comorbidities, median (IQR)	2.0 (1-4)
Heart disease, n (%):	49 (23.5)
Atrial fibrillation, n (%)	33 (15.9)
Ischemic heart disease, n (%)	31 (14.9)
Heart failure, n (%)	13 (6.25)
Interstitial pneumonia, n (%)	186 (89.8)
LUS score, median (IQR)	12 (7-18)
CT severity score, median (IQR)	9 (6-12)
PaO_2/FiO_2, median (IQR)	276 (178-336.5)
ARDS, n (%)	97 (46.9)
Mild	54.2%
Moderate	40.6%
Severe	6.2%
O_2-therapy: n (%)	164 (79.2)
Nasal cannula, n (%)	30 (14.5)
Venturi mask, n (%)	64 (30.9)
High flow nasal cannula, n (%)	65 (31.4)
CPAP, n (%)	5 (2.4)
WBC x mmc, median (IQR)	7340 (5250-10210)
Hb (g/dl), median	13.3
PLT x mmc, median (IQR)	287 (208-342)
CRP, mg/dl, median (IQR)	4.56 (1.8-9.9)
eGFR, median (IQR)	88 (68-100)
ALT x n.v.	1.04
gGT x n.v.	1.39
Bilirubin mg/dl (mean ± sd)	0.72 ± 0.36
d-Dimer, median (IQR)	575 (281-1115)
Fibrinogen, mg/dl, median (IQR)	566 (430-716.5)
Ferritin, mg/dl, median (IQR)	541 (247-1018)

heart disease (heart failure and/or ischemic heart disease and/or atrial fibrillation), liver disease (chronic hepatitis or cirrhosis), solid organ transplantation, active neoplasia, and number of comorbidities. All variables that were significantly associated with mortality at the univariate analysis, after adjustment for age and sex, were included in the multivariate analysis using the multiple logistic regression model to identify independent factors associated with mortality. The relative risk (R-R) of mortality and 95% confidence interval (95% C.I.) for significant associated factors was calculated. A *p*-value of 0.05 was assumed to denote significance.

Results

A total of 208 consecutive COVID-19 patients admitted to our hospital were included in the study. The demographic and clinical characteristics of patients on admission are reported in Table I. The median age was 64 years and 58.6% were male. Active or previous smoking was present in 47.1% of patients and 37% were overweight/obese. At admission, 83% of patients had 1 to 6 comorbidities, median 2.0 (IQR,1-4). The most frequent comorbidities were hypertension (55.8%), type 2 diabetes (24%), chronic kidney failure (36.5%; 38 patients had an eGFR ≤60 mL/min), COPD (14.9%), ischemic heart disease (19.9%), hearth failure (6.25%), atrial fibrillation (15.9%), and active neoplasia (3.8%). Three patients had received solid organ transplantation, and 3 patients were on chronic dialysis. Interstitial pneumonia was present in 89.8% and O_2 therapy was required in 79.2% of patients. The median PaO_2/FiO_2 ratio was 276 (IQR, 178 - 336.5); 34.15% has a PaO_2/FiO_2 ratio ≤220. On admission, ARDS, defined according to Berlin criteria[13], was present in 96 patients (46.1%), and ARDS severity was mild in 54.2%, moderate in 40.6%, and severe in 6.2%.

During hospitalization, 45.4% of patients received non-invasive ventilation (CPAP, PSV) with a median peep of 7 (IQR, 7-8), whereas 11.1% of patients required intubation (IOT) and were transferred to the ICU. None of the patients developed barotrauma-induced lung injury. However, 2 patients, transferred from another hospital, had pneumothorax, pneumomediastinum and subcutaneous emphysema on admission. These 2 patients had undergone NIV with peep >20 in the previous days. The continuous respiratory monitoring made it possible to timely capture the variations in the respiratory function as well as the functioning of the respiratory devices, thus allowing timely intervention.

During hospitalization, 80 patients presented with an arrhythmia, of which 57.5% developed a new onset arrhythmia, while the remaining 42.5% of patients were already chronically affected by arrhythmic disorders. All arrhythmic events were identified early by telemetry, and a prompt treatment made it possible to control the arrhythmic episodes in all cases.

Among our 208 patients, during hospitalization, 21 died (10.1%). Of these, 4 (1.9%) died in primary hospital/sub-intensive care unit, while 17 (8.2%) died after IOT and their moving to the ICU.

Table II. Uni-multivariate analysis of the basal factors associated with in-hospital mortality in 208 consecutive COVID-19 patients.

Patients' characteristics	Univariate analysis		Multivariate analysis			
	Values	p =	O.R.	95% C.I. Lower	Higher	p =
Age, yrs, median (range)						
Deaths: n = 21	75.5 (61-90)		1.14	1.06	1.23	0.001
Alives: n = 187	62.4 (26-93)	0.0001				
Male, n:						
Deaths: n = 16/21	76%		0.24	0.05	1.09	0.06
Alives: n = 107/187	57.2%	0.17				
Overweight/Obesity, n:						
Deaths: n = 8/21	38%		–	–	–	–
Alives: n = 44/187	23.5%	0.28				
Smoke, n:						
Deaths: n = 12/21	57.1%		0.90	0.19	4.19	0.92
Alives: n = 76/187	40.6%	0.052				
Pre-admission days, median (IQR):						
Deaths	5 (2.5 -9.0)		–	–	–	–
Alives	8 (4.0, 11.0)	0.16				
d-Dimer, (ng/ml) median (IQR)						
Deaths	1800 (810 - 3200)		1.0004	1.0002	1.0007	0.001
Alives	524 (270 -1000)	0.00001				
Fibrinogen, (mg/dl): median (IQR)						
Deaths	546 (462- 662)		–	–	–	–
Alives	566 (433 - 1018)	0.77				
CRP, (mg/dl) median (IQR)						
Deaths	6.76 (3.80-12.85)		–	–	–	–
Alives	7.90 (1.64-9.55)	0.054				
Chronic Liver Disease (%)						
Deaths: n = 3/21	14.3%		–	–	–	–
Alives: n = 18/187	9.6%	0.83				
eGFR (ml/min):						
≤60: (n = 38) - deaths: n=8	21%		8.56	2.35	31.19	0.001
>60: (n=170) - deaths: n=13	4.8%	0.03				
Hypertension (%)						
Deaths: n = 16/21	76.2%		–	–	–	–
Alives: n = 100/187	53.5%	0.083				
Type 2 diabetes, (%)						
Deaths: n= 8/21	38%		–	–	–	–
Alives: n= 44/187	23.5%	0.27				
COPD, (%)						
Deaths: n = 8/21	38%		–	–	–	–
Alives: n = 23/187	12.3%	0.004				
PaO_2/FiO_2, median (IQR)						
Deaths	174 (133-257)		0.98	0.98	0.99	0.001
Alives	280 (189-338)	0.002				
CT severity score, median (IQR)						
Deaths	11 (10-14.4)		–	–	–	–
Alives	9 (6-12)	0.02				
LUS score, median (IQR)						
Deaths	14 (7-22)		–	–	–	–
Alives	12 (7.5-18)	0.50				
Heart disease, (%)			1.47	0.45	7.01	0.41
Deaths: n = 13/21	61.9%	0.0001				
Alives: n = 36/187	19.2%					
Heart failure:						
Deaths: n= 6/21	28.6%	0.00001				
Alives: n= 7/187	3.7%					
Ischemic heart disease:						
Deaths: n = 8/21	38%	0.004				
Alives: n = 23/187	12.3%					
Atrial fibrillation:						
Deaths: n = 7/21	33.3%	0.05				
Alives: n = 26/187	13.9%					
Solid organ transplant, (%)						
Deaths: n = 2/21	9.5%		–	–	–	–
Alives: n = 1/187	0.5%	0.05				
Number of comorbidities, median (IQR):						
Deaths	4 (3.0 - 4.5)		1.53	1.03	2.27	0.03
Alives	2 (1.0-3.0)	0.001				

Table III. Relative-Risk of death for the significant baseline factors.

Variable	R-R	95% C.I. Lower	Higher	Z score	p =
Age ≥ 70 yrs	5.44	2.076	14.274	3.446	0.0006
d-Dimer ≥ 1,000 ng/ml	7.53	2.887	19.665	4.127	0.0001
PaO_2/FiO_2 < 200	3.21	1.427	7.230	2.821	0.0048
eGFR ≤60 ml/min	2.91	1.299	6.541	2.594	0.0095
Heart disease	5.27	2.321	11.977	3.972	0.0001
Heart failure	3.66	1.517	8.843	2.887	0.0039
Ischemic heart disease	3.77	1.703	8.349	3.274	0.0011
Atrial fibrillation	3.50	1.556	7.859	3.035	0.0024
Solid organ transplant	7.19	2.902	17.826	4.261	0.0001
Number of comorbidities ≥ 3	2.720	1.488	6.474	2.274	0.0229

Factors at Admission, Associated with In-Hospital Mortality

Table II shows an analysis of the factors present at hospitalization associated with in-hospital mortality from COVID-19. In the univariate analysis, the factors found associated with mortality were: advanced age ($p<0001$), COPD ($p<0.004$), renal insufficiency with eGFR ≤60 mL/min ($p<0.03$), heart disease ($p<0.0001$) [heart failure ($p<0.0001$), ischemic heart disease ($p<0.004$), atrial fibrillation ($p<0.05$)], solid organ transplantation ($p<0.05$), more than 3 comorbidities ($p<0.01$), pneumonia with a high CT score ($p<0.02$) and a low PaO_2/FiO_2 ratio ($p<0.002$); furthermore, some inflammatory indices have been associated with mortality, such as high levels of d-Dimer ($p<0.0001$) and CRP ($p<0.05$). None of the 8 patients with active cancer died.

The multivariate analysis, reported in Table II, shows that the factors, at hospitalization, independently associated with in-hospital mortality were advanced age ($p<0.001$), high serum levels of d-Dimer ($p<0.001$), low PaO_2/FiO_2 ratio ($p<0.001$), eGFR values ≤60 ml/min ($p<0.001$), and a number of comorbidity equal or greater than 3 ($p<0.03$). Among the 3 or more aggregate comorbidities, those with the greatest impact on in-hospital mortality were: hypertension in 71% of cases, heart diseases in 57%, past or present smoking in 57%, vasculopathy in 48%, diabetes in 38%, COPD and obesity in 33%, and liver disease in 14%.

Table III reports the relative risk (R-R) of death associated with the individual risk factors on admission. The R-Rs associated with the independent factors of death were an age equal to or greater than 70 years (R-R, 5.44), a d-Dimer equal to or greater than 1,000 ng/dl (R-R, 7.53), a PaO_2/FiO_2 <200 (R-R, 3.31), an eGFR ≤60 ml/min (R-R, 2.91), and a number of comorbidities equal to or greater than 3 (R-R, 2.72). In addition, among the comorbidities, patients with heart disease showed a high R-R of 5.27. A high risk was also observed in patients with solid organ transplantation (R-R, 7.92) although only 3 patients were present in this subgroup.

Discussion

In this prospective, single-center study, the predictor factors associated with in-hospital mortality of COVID-19 patients admitted during the third pandemic phase were evaluated. The analysis of the case series shows that more than 80% of our hospitalized patients presented a medium/severe disease with a significant proportion of patients (about 75%) requiring high flows of O_2 or NIV. The frequency of comorbidities present at hospitalization was generally not different from that reported in the studies in the first pandemic phase[7,14-16]. The most frequent comorbidity was hypertension (55.8%), followed by overweight/obesity (37%), chronic renal failure (36.5%), diabetes mellitus (25%), chronic heart disease (23.5%), chronic vascular disease (19.7%), chronic respiratory diseases (14.7%), chronic liver disease (11.5%), and active malignancy (3.8%).

The overall mortality in our patients was 10.1% of which 1.9% died in primary hospital/sub-intensive care unit and 8.2% in the ICU. The figure appears to be significantly different from the mortality observed during the first pandemic phase. In fact, a multicentric study (COVOCA) conducted in our region on the data of the first epidemic phase, in a population with characteristics close to our series, had shown a mortality of 23%[1]. The studies conducted during the first phase in Northern Italy have shown in-hospital mortality between 28% and 38%[6-9]. Similarly, studies conducted around the world have reported

an intra-hospital mortality rate of 24-26%[2-4]. The reduction of in-hospital mortality observed in our population could be attributed to several factors. In particular, the improved health care and medical experience acquired as well as the improved therapeutic armamentarium and its proper use for the management of the infections and complications.

Data from our series show that the independent predictors, at admission, of a high risk of in-hospital mortality from COVID 19 were advanced age, particularly patients over 70 years old had a R-R of 5.54 times greater, renal failure, in particular, patients with eGFR ≤60 ml/min showing an increase in the R-R of mortality of 2.91, and the presence of multiple co-morbidities, in particular a number equal to or greater than 3 was associated with an increase in the R-R of 2.72 (Table III). Among the 3 or more co-morbidities present at the same time, in addition to renal failure, chronic cardiovascular diseases (hypertension, heart failure or ischemic heart disease) seem to play an important role in the negative outcome; although smoking, diabetes, COPD and obesity also play a role.

Data from this study referring to the third phase of the pandemic confirm that advanced age is one of the most determinant factors associated with in-hospital death from COVID-19, as reported in the first phase[14-16]. The data were predictable, considering that age is a factor that cannot be modified. Therefore, it is necessary that the health system makes the greatest effort in the active immunization of the population over 60 years old to prevent the high mortality risk from COVID-19 in these subjects. On the other hand, many chronic diseases found to be independently related to COVID 19 mortality in the first phase[17-19] seem to play a less defined role in the third phase of the pandemic. In fact, hypertension, heart diseases, diabetes mellitus, chronic liver diseases, COPD and smoking were not independently associated with mortality in our third phase series; however, they maintain a prognostic role when present in aggregate form with at least 3 chronic conditions. The overall management of COVID-19 has been improved on the basis of the recommendations of the latest scientific evidence which led to a reduction in mortality[10,11,14,16]. In the context of chronic diseases, it should be noted that the presence of severe renal insufficiency (in chronic or non-chronic dialysis), which is a non-modifiable factor, remains independently associated with in-hospital mortality from COVID 19.

In agreement with the studies carried out in the first phase[20,21], another factor independently associated with a significant increase in mortality risk was a value of d-Dimer equal to or greater than 1,000 ng/ml (R-R: 7.53). The data indicate that current management is not optimized for these patients yet. A recent multicenter, randomized study[22] evaluated the use of rivaroxaban in patients with high d-Dimer values, unfortunately showing that the use of NAO is unable to modify mortality rate in these patients. Therefore, further studies will be needed to evaluate new treatments able to improve the prognosis of COVID-19 patients with impaired coagulation state.

Another factor independently associated with an increased risk of mortality, in agreement with the results of the first phase[23,24], was the presence of moderate/severe ARDS at hospitalization. In particular, a PaO_2/FiO_2 ratio less than 200 was associated with an increase in R-R of 3.21. Severe SARS-CoV-2 pneumonia still represents the greatest therapeutic challenge and further studies are needed in order to identify more effective treatments than current ones. For example, preliminary data indicate that anti-inflammatory and/or immunomodulatory drugs could have a favorable impact on the outcomes of severe ARDS associated with SARS-CoV-2. Thus, an optimal intervention protocol that allows to customize the therapy of the individual patient according to his inflammatory state and to the phase of the natural history of the disease appears to be mandatory. In addition, it could be necessary to anticipate hospitalization in selected patients who require home oxygen therapy to initiate early intensive treatment and thus reduce, perhaps, the mortality rate.

It should be emphasized that an important role was played by the continuous monitoring of respiratory function and telemetry. These devices allow to detect early alterations of the respiratory function and to identify early arrhythmic events. We consider continuous monitoring and telemetry to be necessary aids in setting up wards where patients are isolated and contacts with healthcare personnel must obviously be limited. These aids allow healthcare personnel to intervene in a targeted manner in cases that require timely therapeutic intervention with an evident improvement in the outcome.

The limitations of our study can be found in the relatively small sample size, a low number of events and for being an unicentric study. Therefore, some cautions are required in generalizing the results. However, we are confident that the

data are relevant and representative of centers similar to ours. Furthermore, we believe that the fact that the study was conducted in a single center with a standardized management protocol may have been a positive factor aimed at avoiding the confounding variables associated with different management approaches own of the centers involved in the multicenter studies.

Conclusions

The data demonstrate that during the third pandemic phase of the COVID-19 improved management leads to a significant reduction of COVID-19 in-hospital mortality, and especially continuous monitoring and telemetry play an important role. Therefore, we believe it is important that these safeguards are present in the setting up of the COVID operating units. The data also seem to demonstrate that most of the comorbidities are no longer independent predictor of mortality as a consequence of improved management, although many comorbidities continue to play a role when they occur in aggregate form in the same patient. These findings could help in an early risk stratification of patients and, therefore, of those who need more efforts in the care management. Although, some non-modifiable factors, such as advanced age, severe renal failure, and subjects with multiple pathologies continue to be independent predictors for a high mortality risk. Hence, efforts for mass vaccination of these patients need to be implemented. In addition, patients that upon hospitalization had high d-Dimer levels or moderate/severe ARDS continue to have a high risk of mortality and, at present, there is no codified approach for these patients and future studies are needed to optimize management for improve mortality.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for this study.

Authors' Contributions

R. Nevola and L.E. Adinolfi conceived and designed the study. All authors contributed to the preparation of the materials, the conception of the database and the collection of data. The data analysis was done by L.E. Adinolfi and G. Signoriello. The first draft of the manuscript was written by R. Nevola and L.E. Adinolfi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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