ONLINE SUPPLEMENTARY MATERIAL

ACUTE MYOCARDIAL INFARCTION *VERSUS* OTHER CARDIACOVASCULAR EVENTS IN COMMUNITY-ACQUIRED PNEUMONIA

MATERIAL AND METHODS

Data collection

Charts of all patients were abstracted using a standardized form. Information included demographic characteristics, comorbidities, electrocardiogram, clinical, radiological and laboratory results on admission and during hospitalization, severity of the disease on admission, including the pneumonia severity index, CURB-65 score, admission to intensive care unit, and ventilatory and blood pressure support on admission [1,2].

Study definitions

Community-acquired pneumonia was defined as the presence of a new pulmonary infiltrate seen on radiograph or computed tomography scan of the chest within 48 hours after hospitalization *plus* at least one of the following: a) new or increased cough with/without sputum production; b) fever (documented temperature -rectal or oral- ≥ 38.3) or hypothermia (documented temperature –rectal or oral- <36° C); c) evidence of systemic inflammation (such as abnormal white blood cell count -either leukocytosis (>10,000/cm3) or leukopenia (< 4,000/cm^3) - or C-reactive protein or procalcitonin values above the local upper limit.

Severe sepsis was defined by the presence of at least one of the following signs of organ hypoperfusion or organ dysfunction: 1) sepsis-induced hypotension; 2) lactate greater than the upper limits of normal laboratory results; 3) urine output <0.5 mL/kg/hour for >2 hours, despite adequate fluid resuscitation; 4) creatinine >2.0 mg/dL; 5) bilirubin >2 mg/dL; 6) platelet count <100,000; 7) coagulopathy (INR >1.5) [3].

Septic shock was defined as sepsis associated with sepsis-induced hypotension despite adequate fluid resuscitation [3].

Acute respiratory failure was defined as the presence of at least one of the following on admission: 1) partial pressure of oxygen in arterial blood (PaO_2) < 60 mmHg; 2) ratio of PaO_2 and fraction of inspired oxygen (PaO_2/FiO_2) < 250; 3) oxygen saturation < 90%; 4) respiratory acidosis, and 5) ventilatory support. Respiratory acidosis was considered when a pH value on admission of less than 7.35 was identified with a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) ≥ 45 mmHg [4].

Clinical failure. During the first 6 hours after admission to the Emergency Room (ER) / ward patient was stabilized and his "baseline status" was defined. The presence of clinical failure was evaluated after stabilization of the patient in the ER and after her/his admission in the department, and during hospitalization. Clinical failure was identified by the presence of at least one of the following in comparison to baseline or the previous day: 1) acute pulmonary deterioration with the need of either non-invasive or invasive mechanical ventilation (defined as: use of accessory muscles or paradoxical movement during breathing *plus* respiratory rate > 30 b/m *plus* PaO_2/FiO_2 ratio < 250 or a reduction of ≥30% of the basal PaO_2/FiO_2 ratio value or acute respiratory acidosis or increase of 20% of $PaCO_2$ value if prior $PaCO_2$ value was ≥40mmHg) or leading to either non-invasive or invasive mechanical ventilation; 2) acute hemodynamic deterioration with the need of aggressive fluid resuscitation (over 40 ml/kg of

colloids or crystalloids in 4-6 hours), vasopressors or invasive procedures (e.g.: pericardial drainage, electrical cardioversion); 3) in-hospital death [5].

Chronic renal failure was defined in a subject having a creatinine clearance <60 mL/min/1.73 m2 for at least 12 months prior hospitalization.

Coronary artery disease was defined as 1) >50% reduction in luminal diameter of at least one of the three major epicardial coronary arteries, 2) a documented myocardial infarction (MI), or 3) a perfusion abnormality on nuclear imaging in >= 1 coronary artery territory, before hospitalization.

Essential Arterial hypertension was defined in a subject having a systolic blood pressure ≥ 140 mm Hg, or a diastolic blood pressure ≥ 90 mm Hg, or taking anti-hypertensive medications for at least 12 months prior hospitalization.

Hyperlipidemia was defined in a subject having a total cholesterol level above 200 mg/dl and/or taking antihyperlipidemic drugs for at least 12 months prior hospitalization.

Congestive heart failure was defined in a subject in NYHA class II or higher, based on symptoms, signs and objective abnormality on echocardiography, for at least 12 months prior hospitalization [6].

Neurological disease was defined in a subject with a history of a central nervous system malignancy, stroke, head injury, or degenerative neurological disorder diagnosed before hospitalization.

Liver disease was defined in a subject having either cirrhosis or chronic active hepatitis, or primary biliary cirrhosis, with any of the following sequelae: ascites, oesophageal varices, portal hypertension, or active hepatic encephalopathy, diagnosed before hospitalization.

Thrombocytosis was defined as platelet counts > 400,000/L on hospital admission

Microbiological examination

Pleural puncture, tracheobronchial aspirates, and bronchoalveolar lavage fluid, when available, were also collected and cultured. The etiology was considered definite if one of the following criteria was met: positive blood culture in the absence of an apparent extrapulmonary focus; positive bacterial culture of pleural fluid; positive urinary antigen for *Legionella pneumophila* (Binax Now, Trinity Biotech, Bray, Ireland); positive urinary antigen for *Streptococcus pneumoniae* (Binax Now, Emergo Europe, The Netherlands); a bacterial yield in cultures of valid sputum (> 25 polymorphonuclear cells and < 10 epithelial cells per power field, total magnification x 100) of at least 10^6 CFU/mL, tracheobronchial aspirates of at least 10^5 CFU/mL, bronchoalveolar lavage fluid of at least 10^4 CFU/mL and protected specimen brush cultures of at least 10^3 CFU/mL; seroconversion (a 4-fold rise in IgG titers for *C. pneumoniae* [1:512], *L. pneumophila* or a rise in IgM titers for *C. pneumoniae* [1:32] and *M. pneumoniae* [any titer]) occurred. When two or more microbiological causes were present, the patient was considered to have a polymicrobial infection. Patients for whom no microbiological tests were performed, and patients with negative microbiogical results, were considered to have disease of an unknown etiology.

Definitions of cardiovascular events

Criteria for *acute myocardial infarction (AMI)* were defined as: detection of rise and/or fall of troponin with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: 1) symptoms of ischemia; 2) electrocardiogram (EKG) changes indicative of new ischemia (new ST-T changes or new left bundle branch block); 3) development of pathologic Q waves in the EKG;

or 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [7].

Diagnosis of *acute cardiogenic pulmonary edema* was established on the basis of medical history (acute severe dyspnea) and typical physical findings (widespread pulmonary rales), with chest radiography, performed within 6 hours from the event, confirming pulmonary vascular congestion.

Diagnosis of a *new arrhythmia* was established if any of the following was present as new onset: atrial flutter, atrial fibrillation, junctional supraventricular, or ventricular tachycardia.

Diagnosis of an *acute worsening of a long-term arrhythmia* was established if atrial fibrillation was switched to atrial flutter or in the presence of a switch of classes in Lown classification or in the presence of hemodynamic impairment (clinical features of shock and/or systolic blood pressure< 90 mmHg).

Cerebrovascular accident was defined as the development of an embolic, thrombotic, or hemorrhagic vascular accident or stroke with motor, sensory, or cognitive dysfunction that persisted for ≥24 hours, or transient ischemic attack, or reversible ischemic neurologic deficit if confirmed by a neurologist after computed tomography or magnetic resonance imaging scanning [8].

Pulmonary embolism was defined as a chest computed tomography evidence of a thromboembolus occluding the pulmonary trunk or one or both main pulmonary arteries consistent with an acute onset of new or worsening shortness of breath or chest pain without another obvious etiology.

All of the enrolled patients were evaluated on admission and every day during hospitalization to identify those undergoing CVE. If a patient was diagnosed on admission to the hospital as having both CAP and a CVE, the latter was defined to be on hospital admission. Each case of cardiovascular event was presented and discussed to a clinical review committee in each

center, composed of at least three physicians, one of whom was a cardiologist. Electrocardiogram and Troponin T or I were performed for the enrolled patients on hospital admission, and at every moment when clinicians had a clinical suspicion of the presence of a cardiovascular event. Troponin T or I determinations were performed with 3 set (every 6 hours) during the first 24 hours after hospital admission and if a suspicion of AMI was present during the hospital course. Chest radiograph was performed during hospital course if a suspicion of ACPE was present. Computed tomography (CT) of the chest was performed on admission and every time during the hospital course if a suspicion of pulmonary embolism was present. Head CT was performed on admission and every time during the hospital course if a suspicion of CVA was present.

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TABLES

Table A. Baseline demographics, severity of the disease and radiological findings on admission of the three study groups.

CVE: cardiovascular events; AMI: acute myocardial infarction

	Group "AMI" n=21	**Group "Other CVE" n=107**	**Group "No CVE" n=777**	**p** among the three groups	**p** "AMI" vs. "Other CVE"
Demographics, n. (%)					
Female sex	12 (57)	55 (51)	307 (40)	0.021	0.630
Age, median (IQR) years	79 (72-85)	83 (75-88)	75 (64-83)	<0.001	0.258
Body mass index, median (IQR)	25 (22-29)	24 (22-27)	24 (22-27)	0.961	0.781
Active smokers	2 (12)	9 (11)	101 (15)	0.570	0.899
Healthcare-associated pneumonia	7 (33)	18 (17)	109 (14)	0.040	0.081
Nursing Home Residency	4 (19)	8 (7.5)	33 (4.2)	0.004	0.096
Severity on admission, n. (%)					
Ventilatory support°	8 (38)	31 (29)	90 (12)	<0.001	0.406
Blood pressure support§	2 (9.5)	4 (3.7)	20 (2.6)	0.145	0.251

Mental status change	5 (24)	25 (23)	100 (13)	0.007	0.965
PSI Risk Class IV and V	21 (100)	99 (93)	572 (74)	<0.001	0.196
PSI Risk Class V	17 (81)	53 (50)	220 (28)	<0.001	0.007
CURB65 score 3-4-5	12 (57)	55 (51)	252 (32)	<0.001	0.630
Admission to ICU	1 (4.8)	1 (0.9)	10 (1.3)	0.363	0.302
Acute respiratory failure	17 (81)	72 (67)	395 (51)	<0.001	0.214
Severe sepsis	15 (71)	43 (40)	215 (28)	<0.001	0.009
Radiology, n. (%)					
Multilobar infiltrates	4 (21)	28 (27)	162 (22)	0.431	0.577
Bilateral infiltrates	2 (11)	21 (20)	99 (13)	0.127	0.313
Pleural effusion	9 (43)	44 (41)	217 (28)	0.008	0.883

n: number; IQR: 25-75 interquartile range; PSI: pneumonia severity index; ICU: intensive care unit; °either non-invasive or invasive mechanical ventilation; [§]use of vasopressors;

Table B. Comorbidities and home medications of the three study groups.

CVE: cardiovascular events; AMI: acute myocardial infarction

	Group "AMI" n=21	**Group "Other CVE" n=107**	**Group "No CVE" n=777**	**p** among the three groups	**p** "AMI" vs. "Other CVE"
Comorbidities, n. (%)					
Active neoplastic disease	5 (24)	14 (13)	93 (12)	0.256	0.206
Chronic obstructive pulmonary disease	9 (43)	35 (33)	211 (27)	0.155	0.371
Diabetes mellitus	4 (19)	25 (23)	158 (20)	0.755	0.666
Prior cerebrovascular accident	10 (48)	33 (31)	152 (20)	<0.001	0.137
Liver disease	5 (24)	1 (0.9)	42 (5.4)	<0.001	<0.001
Neurological diseases	7 (33)	33 (31)	141 (18)	0.003	0.822
Renal Disease	2 (9.5)	10 (9.3)	64 (8.2)	0.911	0.980
Chronic renal failure	7 (33)	13 (12)	95 (12)	0.016	0.015
Immunosuppression^{+}	6 (29)	14 (13)	98 (13)	0.101	0.074
Family history of coronary artery disease	6 (29)	18 (17)	114 (15)	0.193	0.207
Essential Arterial Hypertension	11 (52)	63 (59)	402 (52)	0.382	0.581
Congestive heart failure	9 (43)	33 (31)	136 (18)	<0.001	0.284
Coronary Artery Disease	8 (38)	29 (27)	126 (16)	0.001	0.310
Prior acute myocardial infarction	4 (19)	19 (18)	80 (10)	0.040	0.888

Atrial fibrillation	6 (29)	27 (25)	115 (15)	0.007	0.749
Hyperlipidemia	7 (33)	19 (18)	126 (16)	0.113	0.105
Medications before admission, n.(%)					
Aspirin	10 (48)	41 (38)	219 (28)	0.020	0.426
Beta-blockers	6 (29)	26 (24)	177 (23)	0.785	0.679
ACE-inhibitors	6 (29)	36 (34)	232 (30)	0.716	0.651
Warfarin	2 (9.5)	5 (4.7)	75 (9.7)	0.242	0.371
Heparin	0 (0)	5 (4.7)	25 (3.2)	0.507	0.312
Antipletelts	1 (4.8)	15 (14)	69 (8.9)	0.177	0.241
Statins	4 (19)	10 (10)	122 (16)	0.300	0.253

n: number; COPD: chronic obstructive pulmonary disease; ACE: angiotensin converting enzyme; [+]Immunosuppression defined as the presence of at least one of the following: active cancer, asplenia, HIV infection

Table C. Clinical and laboratory data on admission of the three study groups.

CVE: cardiovascular events; AMI: acute myocardial infarction

	Group "AMI" n=21	**Group "Other CVE" n=107**	**Group "No CVE" n=777**	**p** among the three groups	**p** "AMI" vs. "Other CVE"
Heart rate, bpm	100 (93-120)	103 (86-120)	95 (82-110)	<0.001	0.909
Heart rate >125 bpm, n.(%)	2 (9.5)	21 (20)	74 (9.6)	0.007	0.263
Respiratory rate, bpm	27 (20-30)	24 (20-30)	22 (18-28)	0.009	0.301
Respiratory rate >30 bpm, n.(%)	7 (37)	26 (28)	123 (19)	0.029	0.439
Systolic blood pressure, mmHg	150 (110-180)	130 (115-154)	130 (115-146)	0.106	0.138
Diastolic blood pressure, mmHg	78 (66-99)	70 (64-87)	70 (60-80)	0.083	0.310
White blood cells, cell/L^{-1}	11655 (7725-14585)	12730 (9600-17015)	11335 (8718-15280)	0.083	0.214
Hemoglobin, mean ± SD g/dL	12.4 ± 1.8	12.7 ± 2.0	12.7 ± 2.0	0.775	0.402
Hematocrit, mean ± SD %	38 ± 6	39 ± 5	38 ± 6	0.519	0.771

Platelets, cell/L^{-1}	293500 (193250-398750)	225000 (163750-320250)	217000 (162000-282000)	0.026	0.249
Platelets <100,000 cell/L^{-1}, n.(%)	1 (5)	2 (1.9)	40 (5.2)	0.328	0.402
Platelets > 450000, n.(%)	4 (20)	4 (3.8)	22 (2.9)	<0.001	0.006
LDL, mg/dL	114 (64-138)	80 (65-109)	89 (66-109)	0.187	0.089
High-density lipoprotein, mg/dL	40 (26-58)	38 (28-52)	36 (23-48)	0.399	0.867
Lactate dehydrogenase, mg/dL	510 (389-725)	391 (321-502)	346 (264-443)	<0.001	0.036
Cholesterol, mean ± SD mg/dL	178 ± 72	148 ± 35	150 ± 51	0.061	0.034
Trygliceride, mg/dL	108 (93-157)	94 (72-117)	99 (77-136)	0.078	0.041
NT-proBNP, pg/mL	2521 (246-12527)	1905 (687-4697)	590 (204-1643)	<0.001	0.600
BUN, mg/dL	61 (44-99)	48 (34-72)	40 (27-57)	<0.001	0.117
Creatinine, mg/dL	1.2 (0.9-1.8)	1.1 (0.9-1.4)	1 (0.8-1.4)	0.028	0.315
Sodium, mEq/L	137 (135-142)	137 (132-140)	137 (134-140)	0.567	0.311
Potassium, mEq/L	4.3 (3.8-	4.1 (3.6-	4 (3.6-4.4)	0.041	0.174

	4.9)	4.5)			
Glucose, mg/dL	168 (132-225)	128 (109-183)	123 (106-155)	<0.001	0.033
pH < 7.35, n.(%)	5 (28)	10 (12)	41 (7.2)	0.004	0.072

Data are presented as median (25-75 interquartile range, IQR), unless otherwise indicated.

n: number; SD: Standard deviation; NT-proBNP: N-terminal of the prohormone brain natriuretic peptide; LDL: low-density lipoprotein; BUN: blood urea nitrogen

Table D. Microbiology and empiric antibiotic therapy of the three study groups.

CVE: cardiovascular events; AMI: acute myocardial infarction

	Group "AMI" n=21	**Group "Other CVE" n=107**	**Group "No CVE" n=777**	**p** among the three groups	**p** "AMI" vs. "Other CVE"
Microbiology, n.(%)					
Isolated pathogen	2 (9.5)	20 (19)	133 (17)	0.595	0.309
Mixed infection	1 (4.8)	2 (1.9)	13 (1.7)	0.568	0.423
Bacteremia	0 (0)	3 (4)	24 (5.2)	0.654	0.481
S. pneumoniae	0 (0)	5 (4.7)	49 (6.3)	0.404	0.312
S. aureus	1 (4.8)	3 (2.8)	16 (2.1)	0.641	0.637
Atypicals	0 (0)	2 (1.9)	27 (3.5)	0.474	0.528
Viruses	0 (0)	1 (0.9)	11 (1.4)	0.796	0.656
Empiric antibiotic treatment, n.(%)					
Fluoroquinolone alone	4 (19)	20 (19)	155 (20)	0.957	0.985
Beta-lactam plus macrolide	8 (38)	49 (46)	342 (44)	0.782	0.494
Beta-lactam plus fluoroquinolone	2 (9.5)	24 (23)	157 (20)	0.393	0.173
At least a macrolide	8 (38)	52 (49)	374 (48)	0.639	0.358
ERS 2011 Guidelines under-treatment	0 (0)	1 (0.9)	6 (0.8)	0.904	0.835

n: number; ERS: European Respiratory Society.

Table E. Findings significantly associated with the occurrence of acute myocardial infarction (AMI), other cardiovascular events (CVE) or any CVE either on admission or during hospitalization at the univariate analysis

	AMI		Other CVE		Any CVE	
	OR (95%CI)	**p**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**p**
Female sex			1.61 (1.08-2.43)	0.019	1.68 (1.15-2.44)	0.006
Age>65years			4.41 (2.19-8.88)	<0.001	4.31 (2.28-8.15)	<0.001
Nursing Home	5.31 (1.69-16.7)	0.001			2.33 (1.17-4.65)	0.013
Acute Respiratory Failure	4.11 (1.37-12.32)	0.006	1.99 (1.27-3.05)	0.001	2.21 (1.48-3.29)	<0.001
Severe sepsis	6.54 (2.50-17.06)	<0.001	1.76 (1.16-2.67)	0.008	2.17 (1.48-3.17)	<0.001
Pleural effusion			1.80 (1.19-2.73)	0.005	1.82 (1.24-2.68)	0.002
Congestive Heart Failure	3.54 (1.46-8.56)	0.003	2.10 (1.34-3.29)	0.001	2.30 (1.52-3.48)	<0.001
Previous CVA	3.74 (1.56-8.96)	0.002	1.83 (1.17-2.87)	0.007	2.08 (1.38-3.13)	<0.001
Coronary artery disease	3.18 (1.29-7.83)	0.008	1.92 (1.20-3.06)	0.005	2.10 (1.37-3.22)	0.001

Atrial Fibrillation			1.94 (1.20-3.14)	0.006	2.00 (1.28-3.11)	0.002
Liver disease	5.47 (1.91-15.65)	<0.001				
Neurological disease			2.01 (1.28-3.15)	0.002	2.05 (1.35-3.11)	0.001
Chronic renal failure	3.59 (1.41-9.12)	0.004				
Immunosuppression	2.77 (1.05-7.31)	0.032				

CVA: cerebrovascular accident

Table F. Baseline demographics, comorbidities, severity of the disease, clinical, laboratory and radiological findings on admission, microbiology, and antibiotic therapy data of the study population according to in-hospital mortality. Group S: patients who survived; Group D: patients who died.

	Group S n=824	**Group D n=81**	**p**
Demographics, n. (%)			
Age, median (IQR) years	76 (64-83)	83 (74-89)	<0.001
Age>65 years	595 (72)	75 (93)	<0.001
Healthcare-associated pneumonia	109 (13)	25 (31)	<0.001
Nursing Home Residency	33 (4)	12 (15)	<0.001
Comorbidities, n. (%)			
Active neoplastic disease	91 (11)	21 (26)	<0.001
COPD	218 (27)	37 (46)	<0.001
Cerebrovascular accident	163 (20)	32 (40)	<0.001
Neurological diseases	157 (19)	24 (30)	0.023
Chronic renal Failure	96 (12)	19 (24)	0.002
Immunosuppression[+]	95 (12)	23 (28)	<0.001
Congestive heart failure	147 (18)	31 (38)	<0.001
Atrial fibrillation	123 (15)	25 (31)	<0.001
Severity on admission, n. (%)			
Ventilatory support°	98 (12)	31 (38)	<0.001
Blood pressure support[§]	12 (1.5)	14 (17)	<0.001
Mental status change	99 (12)	31 (38)	<0.001

PSI Risk Class IV and V	612 (74)	80 (99)	<0.001
PSI Risk Class V	228 (28)	62 (77)	<0.001
CURB65 score 3-4-5	271 (33)	48 (59)	<0.001
Admission to ICU	8 (1)	4 (4.9)	0.017
Acute respiratory failure	414 (50)	70 (86)	<0.001
Severe sepsis	220 (27)	53 (65)	<0.001
Radiology, n. (%)			
Multilobar infiltrates	169 (21)	25 (33)	0.023
Bilateral infiltrates	102 (13)	20 (26)	0.001
Pleural effusion	231 (28)	39 (48)	<0.001
Clinical and laboratory data on admission, median (IQR)			
Heart rate > 125 bpm, n.(%)	77 (9.5)	20 (25)	<0.001
Respiratory rate >30 bpm, n.(%)	128 (19)	28 (42)	<0.001
Systolic blood pressure, mmHg	130 (115-150)	122 (106-140)	0.007
Platelets <100000 cell/L^{-1}, n.(%)	35 (4.3)	8 (10)	0.022
LDH, mg/dL	352 (270-443)	454 (319-707)	<0.001
Blood urea nitrogen, mg/dL	40 (26-57)	69 (48-107)	<0.001
Creatinine, mg/dL	1 (0.8-1.3)	1.3 (0.9-1.9)	<0.001
Glucose, mg/dL	123 (106-158)	136 (114-178)	0.015
pH < 7.35	44 (7.3)	12 (17)	0.006
Empiric antibiotic treatment			
Beta-lactam plus macrolide	373 (46)	26 (32)	0.021
Beta-lactam plus fluoroquinolone	156 (19)	27 (33)	0.002
At least a macrolide	404 (49)	30 (37)	0.036

n: number; IQR: 25-75 interquartile range; PSI: pneumonia severity index; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; [+]Immunosuppression defined as the presence of at least one of the following: active cancer, asplenia, HIV infection; °either non-invasive or invasive mechanical ventilation; [§]use of vasopressors; LDH: lactate dehydrogenase.

FIGURES

Figure A. Flow-chart of the study population

Footnotes: pt: patient; CVE: cardiovascular event; ACPE: acute cardiogenic pulmonary edema; CVA: cerebrovascular accident; AMI: acute myocardial infarction

Appendix

Participating centers: Respiratory Unit, AO San Gerardo, Monza, Italy; Emergency Medicine Unit, IRCCS Fondazione Ospedale Maggiore Policlinico Cà Granda Milan, Italy; Pulmonary Unit, IRCCS Policlinico San Donato, San Donato Milanese, Milano, Italy; Internal Medicine Department, Azienda Ospedaliero-Universitaria "S. Maria della Misericordia", Udine, Italy; Clinic of Respiratory Medicine and Pulmonary Cell Research, University Hospital Basel, Basel, Switzerland; Respiratory Unit, Luigi Sacco Hospital, Milan, Italy; Respiratory Unit, Policlinico di Modena, Modena, Italy; Emergency Department and Respiratory Unit, Department of Pathophysiology and Transplantation, IRCCS Fondazione Ospedale Maggiore Policlinico Cà Granda Milan, Italy