

## Supplementary Online Content

Grasselli G, Greco M, Zanella A, et al; for the COVID-19 Lombardy ICU Network. Risk factors associated with mortality among patients with coronavirus disease 2019 in intensive care units in Lombardy, Italy. Published online July 15, 2020. *JAMA Intern Med*. doi:10.1001/jamainternmed.2020.3539

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This supplementary material has been provided by the authors to give readers additional information about their work.

## **eMethods. Definitions**

### **Definition of drug category according to regional database**

The categories of medications, used in this paper, are defined according to the following list of medications extracted from regional database

Angiotensin-converting-enzyme inhibitors (ACE-I): a patient taking any of the following:

"BENAZEPRIL", "CAPTOPRIL E DIURETICI", "CAPTOPRIL", "CILAZAPRIL E DIURETICI", "DELAPRIL E DIURETICI", "DELAPRIL E MANIDIPINA", "DELAPRIL E DIURETICI", "ENALAPRIL", "ENALAPRIL E DIURETICI", "ENALAPRIL E LERCANIDIPINA", "FOSINOPRIL", "FOSINOPRIL E DIURETICI", "LISINOPRIL", "LISINOPRIL E DIURETICI", "MOEXIPRIL E DIURETICI", "PERINDOPRIL", "PERINDOPRIL, AMLODIPINA E INDAPAMIDE", "PERINDOPRIL E AMLODIPINA", "PERINDOPRIL E BISOPROLOLO", "PERINDOPRIL E DIURETICI", "QUINAPRIL", "QUINAPRIL E DIURETICI", "RAMIPRIL", "RAMIPRIL E AMLODIPINA", "RAMIPRIL E DIURETICI", "VALSARTAN E DIURETICI", "ZOFENOPRIL", "ZOFENOPRIL E DIURETICI", "BENAZEPRIL E DIURETICI", "RAMIPRIL E FELODIPINA"

Angiotensin II receptor blockers (ARB): a patient taking any of the following:

"CANDESARTAN", "EPROSARTAN", "EPROSARTAN E DIURETICI", "IRBESARTAN", "IRBESARTAN E DIURETICI", "LOSARTAN", "LOSARTAN E DIURETICI", "OLMESARTAN MEDOXOMIL", "OLMESARTAN MEDOXOMIL E AMLODIPINA", "OLMESARTAN MEDOXOMIL E DIURETICI", "TELMISARTAN", "TELMISARTAN E DIURETICI", "VALSARTAN", "VALSARTAN E SACUBITRIL", "CANDESARTAN E AMLODIPINA", "CANDESARTAN E DIURETICI"

Beta-blocker: a patient taking any of the following:

"ATENOLOLO", "ATENOLOLO ED ALTRI DIURETICI", "BISOPROLOLO", "BISOPROLOLO E TIAZIDI", "CARVEDILOLO", "METOPROLOLO", "NEBIVOLOLO", "NEBIVOLOLO E TIAZIDI", "PROPRANOLOLO", "SOTALOLO"

Anti-hypertensive drugs: a patient taking any of the following. This category was not used as a drug category, but to define hypertension (see comorbidities)

"AMLODIPINA", "BARNIDIPINA", "CLONIDINA", "DILTIAZEM", "DOXAZOSIN", "EPLERENONE", "FELODIPINA", "LACIDIPINA", "LERCANIDIPINA", "MANIDIPINA", "MOXONIDINA", "NIFEDIPINA", "VERAPAMIL"

Plus drugs comprised under categories ACE-I / ARB / Beta blockers

Statin: a patient taking any of the following:

"ATORVASTATINA", "ATORVASTATINA, AMLODIPINA E PERINDOPRIL", "FLUVASTATINA", "LOVASTATINA", "PRAVASTATINA", "ROSUVASTATINA", "ROSUVASTATINA E EZETIMIBE", "SIMVASTATINA", "SIMVASTATINA ED EZETIMIBE"

Corticosteroids: a patient taking any of the following:

BETAMETASONE", "BETAMETASONE ED ANTIBIOTICI", "BUDESONIDE", "CORTISONE", "DESAMETASONE", "METILPREDNISOLONE", "METILPREDNISOLONE ACEPONATO", "PREDNISONE", "TRIAMCINOLONE"

Immunosuppressive agent: a patient taking any of the following:

"AZATIOPRINA", "CICLOSPORINA", "EVEROLIMUS", "TACROLIMUS", "LEFLUNOMIDE", "SIROLIMUS"

Or a drug comprised under category steroids

Diuretics: a patient taking any of the following:

"ACETAZOLAMIDE", "CANRENOATO DI POTASSIO", "CANRENONE", "CLORTALIDONE", "FUROSEMIDE",  
"FUROSEMIDE E FARMACI RISPARMIATORI DI POTASSIO", "IDROCLOROTIAZIDE",  
"IDROCLOROTIAZIDE E FARMACI RISPARMIATORI DI POTASSIO", "INDAPAMIDE",  
"SPIRONOLATTONE", "TORASEMIDE")

Antiplatelet medications: a patient taking any of the following:

"ACIDO\_ACETILSALICILICO", "CLOPIDOGREL", "PRASUGREL", "TICAGRELOR", "TICLOPIDINA"

Anticoagulants: a patient taking any of the following:

"ACENOCUMAROLO", "APIXABAN", "BEMIPARINA", "DABIGATRAN\_ETEXILATO", "EDOXABAN",  
"ENOXAPARINA", "EPARINICI", "FONDAPARINUX", "NADROPARINA", "PARNAPARINA",  
"RIVAROXABAN", "WARFARIN"

## Definition of comorbidities from regional database

Comorbidities used in this study are derived from regional database as follows

	Hypertension	hypercholesterolemia	Diabetes type 2	Cardiovascular disease	Malignancy	COPD	CKD	LIVER DISEASE	Other
ARTERIAL HYPERTENSION	1								
HYPERCHOLESTEROLEMIA, FAMILIAR AND NOT		1							
DIABETES MELLITUS TYPE 2			1						
ISCHEMIC CARDIOMYOPATHY				1					
NON ARRHYTHMIC CARDIOMIOPATHY				1					
ARRHYTHMIC CARDIOMIOPATHY				1					
HYPOTHYROIDISM									1
NEOPLASIA, FOLLOW-UP					1				
NEOPLASIA, REMISSION					1				
ACTIVE NEOPLASIA					1				
HEART FAILURE				1					
COPD						1			
CHRONIC KIDNEY DISEASE							1		
CHRONIC HEPATITIS								1	
ASTHMA									1
CEREBRAL VASCULOPATHY									1
ARTERIAL VASCULOPATHY									1
VALVULAR CARDIOMYOPATHY				1					
DIABETES MELLITUS TYPE 2, COMPLICATED			1						
HASHIMOTO THYROIDITIS									1
VENOUS VASCULOPATHY									1
EPILEPSY									1
RHEUMATOID ARTHRITIS									1
BASEDOW- GRAVES DISEASE AND HYPERTHYROIDISM									1
PSORIASIS AND PSORIATIC ARTHRITIS									1
INACTIVE TRANSPLANT									1
HEPATIC CIRRHOSIS								1	

CROHN DISEASE AND ULCERATIVE COLITIS (IBD)									1
HIV POSITIVE AND OVERT AIDS									1
PARKINSON E PARKINSONISMS									1
RESPIRATORY FAILURE/ OXIGEN THERAPY									1
SYSTEMIC LUPUS ERYTHEMATOUS									1
NERVOUS SYSTEM AND SENSORY ORGANS DISEASES									1
MIASTENIA GRAVIS									1
HYPER AND HYPOPARATHYROIDI SM									1
OSTEOMUSCULAR AND CONNECTIVE TISSUE DISEASES									1
ENDOCRINE, NUTRITIONAL AND METABOLIC DISEASES									1
MULTIPLE SCLEROSIS									1
DIABETES MELLITUS TYPE 1, COMPLICATED									1
DIABETES MELLITUS TYPE 1									1
CARDIOVASCULAR DISEASES									1
CONGENITAL MALFORMATIONS									1
CHRONIC PANCREATITIS									1
AUTOIMMUNE HAEMOLYTIC ANAEMIAS									1
DIALYSIS							1		
GASTROINTESTINAL DISEASES									1
SYSTEMIC SCLEROSIS									1
ANKYLOSING SPONDYLITIS									1
ACTIVE TRANSPLANT									1
SKIN AND HYPODERMIC TISSUE DISEASE									1
CUSHING SYNDROME									1
DEMENTIA									1
SJOGREN DISEASE									1

HEMATIC AND HEMATOPOIETIC ORGANS DISEASE									1
ADDISON SYNDROME									1
TUMORS					1				

Rows are comorbidities from database. Columns are categorical variables used in this paper, as derived from original comorbidities

## Definition of main comorbidities

Main comorbidities, not reported under the category “Other”, had the following definitions in the database, publicly reported at

[https://www.dati.lombardia.it/stories/s/Modello-lombardo-per-la-presenza-in-carico\\_20180222/ya5j-7avn](https://www.dati.lombardia.it/stories/s/Modello-lombardo-per-la-presenza-in-carico_20180222/ya5j-7avn)

(website in Italian only, accessed 10th may 2020)

### ARTERIAL HYPERTENSION

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemptions codes: 031.401, 031.405, D31.401, D31.405, 0031, 0031.405.0, 031.405.0)

Hospitalization in the last 5 years with an ICD9 code 401, 403, 405 diagnosis

Hospitalization in the last 5 years with a DRG code type (134)

Medications prescribed during the last year presenting the following ATC code (C02AC01, C02CA04, C03, C07, C08C, C09 (DDD>50%))

Hypertension was redefined as arterial hypertension plus any patient taking anti-hypertensive medications (see drug categories above)

### HYPERCHOLESTEROLEMIA

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemption code: 025\*)

Hospitalization in the last 5 years with an ICD9 code 272.0, 272.2, 272.4, 272.9 diagnosis

Medications prescribed during the last year presenting the following ATC code (C10AA (DDD>50%))

### DIABETES MELLITUS TYPE 2, UNCOMPLICATED

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemption code: 013.250, only when the latter is given to patients  $\geq$  35 years old)

Hospitalization in the last 5 years with an ICD9 code 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32 diagnosis

Hospitalization in the last 5 years with a DGR code type (294)

Medications prescribed during the last year presenting the following ATC code (A10B\* (DDD>50%))

### DIABETES MELLITUS TYPE 2, COMPLICATED

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Hospitalization in the last 5 years with an ICD9 code 250.42, 250.40, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92, 362.01-363.07, 357.2 diagnosis

Hospitalization in the last 5 years with a DRG code type (285)

Medications prescribed during the last year presenting the following ATC code (N03AX16, N03AX12 (DDD>30%))  
Outpatient visit performing ambulatory performances type 1433, 1434, 1475, 96591, 96592, 96593, 96594, 96595, 96596)

## CARDIOVASCULAR DISEASES

### ARTERIAL VASCULOPATHY

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemptions codes: 02.440, 002.441.2, 002.441.4, 002.441.7, 002.441.9, 002.442, 002.444, 002.447.0, 002.447.1, 002.447.6)

Hospitalization in the last 5 years with an ICD9 code 440, 441, 442, 443.1, 443.2, 444, 445, 447 diagnosis

Hospitalization in the last 5 years with a surgical intervention having code: 3924, 3925, 3926, 3950, 3951, 3952, 3954, 3956, 3957, 3958, 3971, 3972, 3973, 3974, 3979, 3990)

### HEART FAILURE

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemption code: 021.428)

Hospitalization in the last 5 years with an ICD9 code 428 diagnosis

Medications prescribed during the last year presenting the following ATC code (C09A, C09C, (DDD>50%) C03CA, C03CB, C03EB (DDD>50%))

### VALVULAR CARDIOMYOPATHY

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemptions codes: 002.394, 002.395, 002.396, 002.397, 002.424, 002.745, 002.746, 002.747;002.V42.2, 002.V43.3)

Hospitalization in the last 5 years with an ICD9 code 394, 397, 745, 747, V42.2, V43.3 diagnosis

Hospitalization in the last 5 years with a surgical intervention having code: 35

### ISCHEMIC CARDIOMYOPATHY

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemptions codes: 002.414)

Hospitalization in the last 5 years with an ICD9 code 410, 414 diagnosis

Hospitalization in the last 5 years with a surgical intervention having code: 36

Medications prescribed during the last year presenting the following ATC code (C01DA\*(DDD>50%))

### ARRHYTHMIC CARDIOMYOPATHY

Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemptions codes: 002.426, 002.427, 002.V45.0)

Hospitalization in the last 5 years with an ICD9 code 426, 427, V45.0 diagnosis

Hospitalization in the last 5 years with a surgical intervention having code: 3765, 3766, 3768, 3770, 3787, 3789, 3796

Medications prescribed during the last year presenting the following ATC code (C01B\*(DDD>50%))

Outpatient visit performing ambulatory performance type 89481



## NON-ARRHYTHMIC CARDIOMYOPATHY

### Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemptions codes: 031.402, 031.403, 002.416, 002.417, 002.429.4, 0031.402, 0031.403)

Hospitalization in the last 5 years with an ICD9 code 402, 404, 415, 416, 417, 425, 4294 diagnosis

Medications prescribed during the last year presenting the following ATC code (C02KX01, C02KX02, C02KX03, G04BE03, G04BE08, B01AC09 (DDD>50%))

## MALIGNANCY

### ACTIVE NEOPLASIA

#### Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemption code: 048)

Hospitalization in the last 5 years with an ICD9 code 140, 208, V580, V581 diagnosis

Hospitalization in the last 5 years with a surgical intervention having code: 9925

Medications prescribed during the last year presenting the following ATC code (L01\* (excluding L01AB01 and L01AA01))

Outpatient visit performing ambulatory performances type 9925, 9224, 92251, 92271, 92273, 92275, 92283, 92284, 92285, 92286, 38991, 38992, 8901M, 897C1, 9229H, 9229J, 9229K, 9229L, 9229M, MAC01, MAC02, MAC03, MAC04)

### NEOPLASIA, FOLLOW UP

#### Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemption code: 048)

Hospitalization in the last 5 years with an ICD9 code 140, 208, V580, V581 diagnosis

Hospitalization in the last 5 years with a surgical intervention having code: 9925

Medications prescribed during the last year presenting the following ATC code (L01\* (excluding L01AB01 and L01AA01))

Outpatient visit performing ambulatory performances type 9925, 9224, 92251, 92271, 92273, 92275, 92283, 92284, 92285, 92286, 38991, 38992, 8901M, 897C1, 9229H, 9229J, 9229K, 9229L, 9229M, MAC01, MAC02, MAC03, MAC04)

### NEOPLASIA, REMISSION

#### Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions being at list 5 year active and given in the last 10 years (exemption code: 048)

Hospitalization in the last 10 years, but over the 5<sup>th</sup> year since diagnosis, with an ICD9 code 140, 208, V580, V581 diagnosis

Hospitalization in the last 10 years, but over the 5<sup>th</sup> year since diagnosis, with a surgical intervention having code: 9925

Medications prescribed during the last 10 years, but over the 5<sup>th</sup> year since diagnosis, presenting the following ATC code (L01\* (excluding L01AB01 and L01AA01))

Outpatient visit performing ambulatory performances type 9925, 9224, 92251, 92271, 92273, 92275, 92283, 92284, 92285, 92286, 38991, 38992, 8901M, 897C1, 9229H, 9229J, 9229K, 9229L, 9229M, MAC01, MAC02, MAC03, MAC04)

## COPD

### Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemption code: 057)

Hospitalization in the last 5 years with an ICD9 code 491, 492, 494, 496 diagnosis

Medications prescribed during the last year presenting the following ATC code (R03\* (DDD>30%) for patients over >=45 years old)

## CHRONIC KIDNEY DISEASE

### Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemptions codes: 023, 031.403, 031.404, 0031.403, 0031.404, 061, 062)

Hospitalization in the last 5 years with an ICD9 code V56, 585, 586 diagnosis

Hospitalization in the last 5 years with a DRG code: 316, 317

Medications prescribed during the last year presenting the following ATC code (V03AE02, V03AE03, V03AE01, H05BX01, H05BX02 (DDD>50%))

## DIALYSIS

### Tracers

Outpatient visit performing at least 70 ambulatory performances type 3995, 5498

## LIVER DISEASES

### LIVER CIRRHOSIS

#### Tracers

We associate this pathology to an assisted patient if, at least, one of the following conditions is fulfilled:

Medical exemptions given in the last 10 years (exemption code: 008)

Hospitalization in the last 5 years with an ICD9 code 571.2, 571.5, 571.6, 571.8, 572.3, 456.0, 456.1, 456.2 diagnosis

## CHRONIC HEPATITIS

### Tracers

We associate this pathology to a patient if, at least, one of the following conditions is fulfilled:

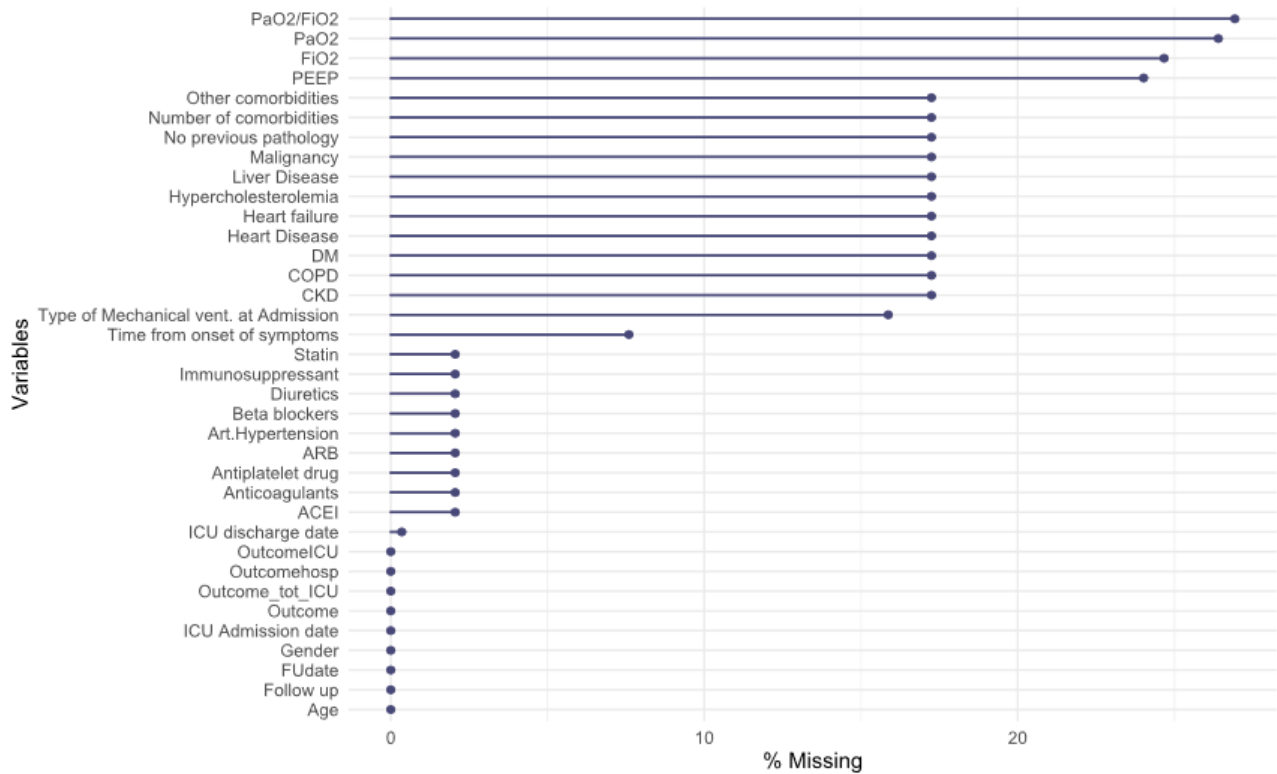
Medical exemptions given in the last 10 years (exemption code: 016)

Hospitalization in the last 5 years with an ICD9 code 070 diagnosis

Medications prescribed during the last year presenting the following ATC code (L03AB04, L03AB05, L03AB06, L03AB09, L03AB10, L03AB11, L03AB12, L03AB60, L03AB61 (DDD>50%), J05AE14, J05AX16, J05AX68, J05AX67, J05AX14, J05AX65, J05AX15)

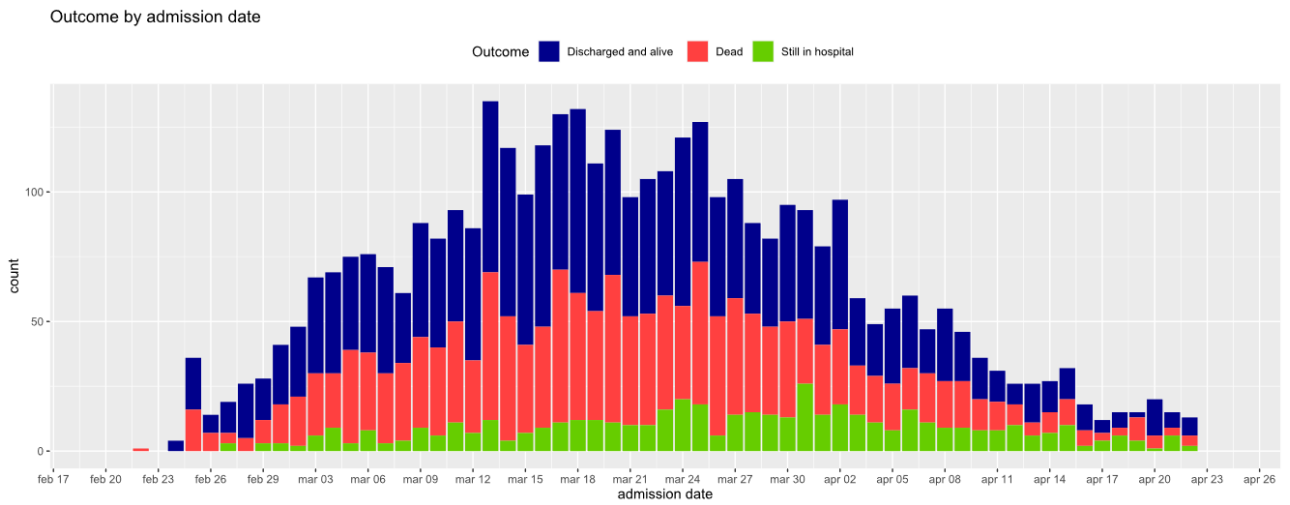
**eFigure 1. Missing Data**

Percentage of missing data for physiological variables, comorbidities, and medications are reported

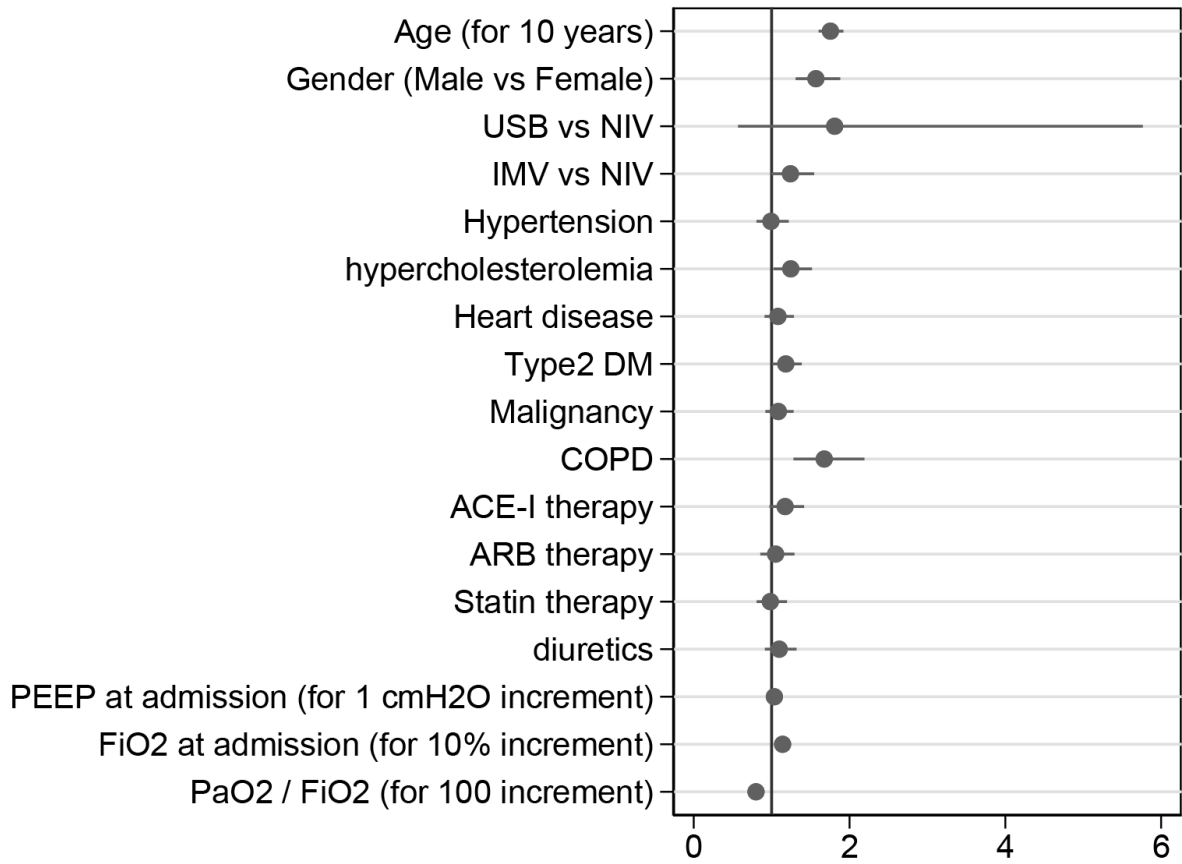


DM=Diabetes Mellitus, COPD= chronic obstructive pulmonary disease, CKD= chronic kidney disease, ARB=angiotensin receptor blocker, ACE-I=Angiotensin I Converting Enzyme. ICU discharge date includes missing data due to patients still in ICU

## eFigure 2. Outcomes According to ICU Admission Date

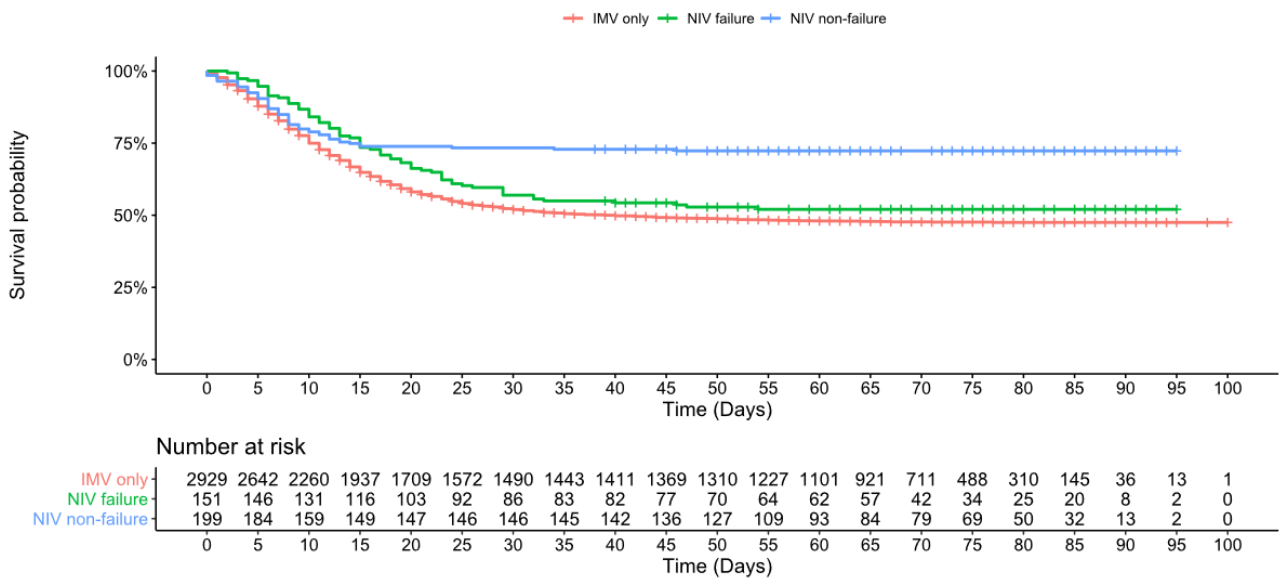


**eFigure 3. Multivariable Model Including Baseline Characteristics, Comorbidities, Medications, and Physiological Variables at Admission**



### eFigure 4. Survival According to Use of Noninvasive Ventilation at Admission

NIV Non-failure, vs NIV failure vs IMV



**eTable 1. Different Characteristics of Patients According to Noninvasive Ventilation or Invasive Mechanical Ventilation at Admission**

	n	NIV (n=350)	IMV (n=2929)	<i>P</i> NIV vs IMV
		Median (IQR)	Median (IQR)	
AGE	3279	62 (53-70)	63 (56-69)	0.37
PaO <sub>2</sub>	2895	88 (71-110)	95 (77-130)	<0.001
FiO <sub>2</sub>	2953	60 (50-80)	70 (60-90)	<0.001
PaO <sub>2</sub> /FiO <sub>2</sub>	2882	144 (104-200)	145 (102-201)	0.12
PEEP	3020	10 (10-14)	13 (11-15)	<0.001
Hazard ratio for mortality*	127 events for NIV, 1514 events for IMV	0.62 (0.52-0.75)	1.6 (1.34-1.92)	<0.001

\* =Non-invasive mechanical ventilation, IMV=Invasive mechanical ventilation

**eTable 2. Previous Medication Use in the Overall Population and in the Subpopulation of Patients With History of Hypertension**

<b>Overall population</b>				
	Number of events	Event ratio*	Hazard ratio	<i>P</i>
Ace-I	435	17.6 (15.9-19.3)	1.58 (1.42-1.75)	<0.001
ARB	404	15.9 (14.4-17.6)	1.43 (1.28-1.6)	<0.001
B-Blockers	427	17.5 (15.9-19.2)	1.6 (1.44-1.78)	<0.001
Statins	479	19.4 (17.7-21.2)	1.76 (1.59-1.95)	<0.001
Immunosuppressors <sup>a</sup>	170	13.4 (11.5-15.6)	1.18 (1.01-1.38)	0.038
Diuretics	137	19.8 (16.6-23.4)	1.68 (1.41-2.0)	<0.001
Anti-platelets drugs	276	21.2 (18.7-23.8)	1.81 (1.59-2.06)	<0.001
Anticoagulants	144	14.8 (12.5-17.4)	1.29 (1.09-1.53)	0.003
<b>Population of hypertensive patients</b>				
	Dead N=924 (57.5%)	Alive N=684 (42.5%)	Total N= 1608	<i>P</i>
ACE-I	435	17.6 (15.9-19.3)	1.15 (1.01-1.3)	0.033
ARB	404	15.9 (14.4-17.6)	1.01 (0.89-1.15)	0.9
B-Blockers	427	17.5 (15.9-19.3)	1.18 (1.04-1.34)	0.013
Statins	406	20.6 (18.7-22.7)	1.42 (1.25-1.61)	<0.001
Diuretics	132	20.7 (17.3-24.6)	1.31 (1.09-1.58)	0.004

\*Event ratio per 1000 patient days. ARB=angiotensin receptor blocker, ACE-I=Angiotensin I Converting Enzyme <sup>a</sup>95% of which were corticosteroids