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Association of comorbidities with clinical outcomes in patients after acute myocardial infarction ☆

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ABSTRACT

Background: Multimorbidity becomes more prevalent in patients admitted for acute myocardial infarction (AMI). We investigated the association of an increasing number of comorbidities with the excess risk of in-hospital mortality and other clinically outcomes in hospitalized AMI patients.
Methods: In this population-based cohort study, we analyzed 104'906 admissions for AMI between 2012 and 2018 in Switzerland. We stratified patients based on four different age categories and investigated the association of the number of five common comorbidities (diabetes, chronic kidney-, chronic obstructive pulmonary-, cerebrovascular-, and peripheral artery disease) and risk of in-hospital mortality and other outcomes.
Results: A total of 5'029 admitted AMI patients (4.8%) died during the hospital stay. We found a stepwise increase in mortality risk with each additional comorbidity. Compared to AMI patients with no comorbidity, comorbid patients had a 26% increased risk for mortality (adjusted odds ratio [OR] 1.26, 95% confidence interval [CI] 1.20 to 1.33) with a pronounced association in younger patients. The overall risk for ICU admission, prolonged length of hospital stay (LOS), and 30-day readmission was higher in comorbid patients as compared to those without a comorbidity of interest (ICU: OR 1.19, 95% CI 1.16 to 1.22; LOS: OR 1.84, 95% CI 1.79 to 1.89; Readmission: OR 1.23, 95% CI 1.19 to 1.28), respectively. Again, the association of the numbers of prevalent comorbidities with adverse outcomes was strongest in the youngest patient population.
Conclusions: In patients with AMI, the burden of comorbidities has a strong association with in-hospital mortality and other adverse outcomes – especially in younger patients.

1. Introduction

As the western population is aging, multimorbidity gains increasing importance with significant health care implications [2,3]. Beside patients, also physicians and hospitals are extensively challenged to overcome this burden of multimorbidity [4]. Whereas the majority of multimorbid patients are older, there is cumulative evidence that even younger patients are progressively confronted with multiple chronic disease conditions [5]. Among patients admitted for an acute myocardial infarction (AMI), around 65% are younger than 75 years [6]. Younger comorbid patients with two, three or more chronic diagnoses are at higher risk for adverse outcomes [5]. Importantly, these patients had a higher amount of hospital admissions as well as hospitalized days compared with older comorbid patients. Regardless a lower overall baseline mortality in younger patients, they had a larger increase in risk over time compared with older patients and the same number of comorbidities [5]. Similar, a large cohort study from the United States found that there was an attenuation of the effect having more chronic disease conditions on mortality in older patients but not in younger ones [7]. The fact that more than half of patients admitted for an AMI have one or more non-cardiovascular comorbidity is of high interest as it is associated with increased length of hospital stay (LOS) and lower survival [8]. Given the high prevalence of acute coronary syndromes in younger patients we aimed to explore the association of five common non-cardiovascular comorbidities (diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular disease, and

☆ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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peripheral artery disease) among different age categories in patients admitted for AMI.

2. Methods

2.1. Study design and data source

This nationwide, population-based cohort study analyzed administrative data collected by the Federal Statistical Office (Bundesamt für Statistik) from January 1st, 2012 to November 30th, 2018. The database included Swiss inpatient discharge records from acute care-, general-, and specialty hospitals, excluding hospital units of post-acute care institutions, regardless of payer, and thus creates a near 100 percent sample of inpatient discharges in Switzerland. The database reflects information captured for billing purposes at hospital level including ICD-10 (International Classification of Diseases, tenth revision, German Modification) codes of all reported diagnoses.

2.2. Study population

We selected all adult (≥18 years) medical inpatient discharge records with a main diagnosis of AMI resulting in a total of 104'906 de-identified hospitalized cases. We applied the following ICD-10 (International Classification of Diseases, tenth revision, German Modification) codes: I21.0 (acute transmural myocardial infarction of anterior wall), I21.1 (acute transmural myocardial infarction of inferior wall), I21.2 (acute transmural myocardial infarction of other sites), I21.3 (acute transmural myocardial infarction of unspecified site), I21.4 (acute subendocardial myocardial infarction), I21.9 (acute myocardial infarction, unspecified), and I22 (subsequent myocardial infarction). Codes from I21.0 to I21.3 were subsumed as ST-elevating myocardial infarctions (STEMI), I21.4 represents non-ST-elevating myocardial infarctions (NSTEMI), and the codes I21.9 and I22 were considered as non-specified myocardial infarctions ("other"). According to the SwissDRG definition, all admissions after 18 days from discharge or admissions into another hospital were evaluated as another index hospitalization. Therefore, a single patient may have more than one index admission in the study period [9]. Medical cases with AMI were defined as encoded by the Federal Statistical Office. Thus, gynecology and obstetrics, pediatrics, ophthalmology, intensive care, otolaryngology, surgery, psychiatry, dermatology and venerology, radiology, geriatrics, rehabilitation and emergency-center patient records were excluded. We formed four age-groups with similar numbers of patients (<60 years, ≥60-69, 70–79 and ≥80 years) for further stratification of our analysis.

We selected comorbidities by their relevance in the setting of an AMI and according to commonly targeted comorbidities in cardiovascular studies [10–13]. Based on ICD-10 codes, we included the following five comorbidities of interest: chronic kidney disease (CKD, N18), diabetes mellitus (DM, E10-14), cerebrovascular disease (CVD, I60-I68), chronic obstructive pulmonary disease (COPD, J44) and peripheral arterial disease (PAD, I70.2).

We coded information on treatment procedures according to the Swiss operation classification system (CHOP) and classified the following CHOP-codes for percutaneous coronary intervention (PCI) [14]: 00.45–00.48 (one, two, three, four or more stents inserted), 36.06 (insertion of non-drug-eluting coronary artery stents), 36.07 (insertion of drug-eluting coronary artery stents), 00.66 (percutaneous transluminal coronary angioplasty or coronary atherectomy), 36.0 (removal of coronary artery obstruction and insertion of stents), 37.2 (right, left or combined heart catheter) and 88.5 (coronary angiography).

Institutional review board approval, including waiver of the requirement of participant informed consent, was provided by institutional review board (IRB) of North-western Switzerland as the data was deidentified (AG/SO 2009/074 and EKNZ BASEC PB_2017-00449). The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

2.3. Study outcomes

We first analyzed time-dependent incidence of AMI and showed time trends for all-cause in-hospital mortality, length of hospital stay (LOS), admission to intensive care unit (ICU), and all-cause 30-day readmission rates over the whole study period.

To investigate the overall and age-dependent excess risk of the selected comorbidities among hospitalized patients with AMI, we defined the following outcomes: The first outcome was all-cause in-hospital mortality. Secondary outcomes were LOS above median, ICU admission, and 30-day all-cause readmission rates. Regarding LOS, we calculated the median for each age-stratified group and created a binary variable for exceeding the median of each group. Information on status of readmission was available for each hospitalization. Readmissions were always attributed to the discharging hospital and admissions with transfer into another hospital were considered as a single episode of care.

2.4. Statistical analysis

We cross tabulated patient characteristics of all included hospitalizations by age-groups. We did descriptive statistics to overview of the overall, time- and age-dependent incidence of cases hospitalized with AMI. The index hospitalization was the unit of analysis.

Associations of the number of comorbidities with in-hospital mortality, LOS, ICU admission, and 30-day readmission rates were assessed using a multivariable logistic or linear regression model adjusted for sex, month and year of admission, domesticity, nationality, type of hospital, type of infarction, CKD, DM, CVD, COPD, PAD, Charlson Comorbidity Index (CCI, excluding comorbidities of interest) [15] and PCI. We included terms of interaction to check for age-stratified subgroup effects and effect modification was calculated by Mantel-Haenszel test of homogeneity.

Significance was based on 95% confidence intervals (CIs). Statistical analyzes and graphical visualizations were performed using the statistical software Stata, version 15.1 (StataCorp, LLC).

3. Results

3.1. Study population

From January 1st, 2012 through November 30th, 2018, we identified a total of 104'906 admissions meeting our inclusion criteria. Table 1 shows baseline characteristics stratified by four age-groups, of whom 28.9% were younger than 60 years, 23.0% were between 60 and 69 years old, 23.6% between 70 and 79 years, and 24.5% 80 years and older. The male proportion continuously decreased from 83.9% in the youngest to 50.9% in the oldest patient group. The most prevalent comorbidity in younger patients was diabetes mellitus (12.8%), whereas chronic kidney disease was most common in the oldest patient group (30.7%).

We found a continuous increase of hospitalized patients with AMI during the observed time period. In the beginning of 2012, 1'195 hospitalizations per month were nationally coded for myocardial infarction, in the end of 2018 the number raised to 1'358 per month (+13.6% over seven years). This increase in coding

Table 1
Baseline Table with patient characteristics.

	age-group 1		age-group 2		age-group 3		age-group 4		p-value
	< 60 years		≥ 60 to < 70 years		≥ 70 to < 80 years		≥ 80 years		
Socio-demographics									
Hospitalizations, n (%)	30'368	(28.9)	24'078	(23)	24'758	(23.6)	25'702	(24.5)	
Male gender, n (%)	25'483	(83.9)	18'495	(76.8)	16'350	(66)	13'083	(50.9)	<0.001
Domestic, n (%)	21'183	(69.8)	19'756	(82.1)	21'191	(85.6)	23'457	(91.3)	<0.001
Tertiary hospital, n (%)	23'963	(78.9)	18'820	(78.2)	19'021	(76.8)	19'124	(74.4)	<0.001
Secundary hospital, n (%)	5'647	(18.6)	4'643	(19.3)	5'137	(20.7)	5'821	(22.6)	
Morbidity									
Myocaridal infarction, n (%)									<0.001
NSTEMI	13'566	(44.7)	12'605	(52.4)	14'945	(60.4)	16'897	(65.7)	
STEMI	16'292	(53.6)	11'030	(45.8)	9'314	(37.6)	7'930	(30.9)	
other types	510	(1.7)	443	(1.8)	499	(2)	875	(3.4)	
Diabetes mellitus, n (%)	3'897	(12.8)	4'843	(20.1)	6'137	(24.8)	5'823	(22.7)	<0.001
Chronic kidney disease, n (%)	601	(2)	1'436	(6)	3'788	(15.3)	7'884	(30.7)	<0.001
Chronic obstructive pulmonary disease, n (%)	454	(1.5)	1'011	(4.2)	1'605	(6.5)	1'363	(5.3)	<0.001
Cerebrovascular disease, n (%)	228	(0.8)	435	(1.8)	731	(3)	838	(3.3)	<0.001
Peripheral arterial disease, n (%)	377	(1.2)	800	(3.3)	1'246	(5)	1'508	(5.9)	<0.001
Charlson comorbidity index, mean (SD)	1.42	(0.89)	1.78	(1.3)	2.29	(1.67)	2.81	(1.75)	<0.001
Intervention									
Percutaneous coronary intervention, n (%)	18'379	(60.5)	14'290	(59.3)	13'273	(53.6)	9'278	(36.1)	<0.001
Patient outcomes									
In-hospital mortality, n (%)	345	(1.1)	525	(2.2)	1'078	(4.4)	3'081	(12)	<0.001
Admission to intensive care unit, n (%)	11'528	(38)	9'219	(38.3)	9'352	(37.8)	6'922	(26.9)	<0.001
Length of stay, mean (SD)	4.10	(4.39)	4.61	(5.06)	5.76	(6.33)	7.55	(7.42)	<0.001
30-day readmission, n (%)	2'728	(9)	2'422	(10.1)	2'741	(11.1)	2'559	(10)	<0.001

was solely due to the rising incidence of non-ST-elevating infarctions (NSTEMI) while the incidence of ST-elevating infarctions (STEMI) remained stable during the observed time (data not shown). During the seven years period, we found a decrease in in-hospital mortality (5.5% to 3.9%), ICU admission rate (38.4% to 31.2%), LOS (6.0 days to 4.7 days), and 30-day readmission rate (10.3% to 9.5%, Fig. 1).

3.2. General excess risk of patient outcomes

Fig. 2 shows the adjusted odds ratios for in-hospital mortality, ICU admission, LOS above median, and 30-day readmission, according to age-groups and the number of comorbidities in AMI patients. There was a similar association over all studied outcomes between the four age groups.

Patients admitted for an AMI who were 80 years of age or older had the lowest incremental risk of in-hospital-mortality, but similar risks for ICU admission, a prolonged LOS, and 30-day readmission as compared with the youngest patient population. Based on term for interaction, age was found as a significant effect modifier ($p < 0.001$).

Fig. 3 visualizes the association of single comorbidities and predefined patient outcomes compared to the patient population without the respective comorbidity. In general, we found a stepwise decrease in risk of adverse clinical outcomes with every next age category.

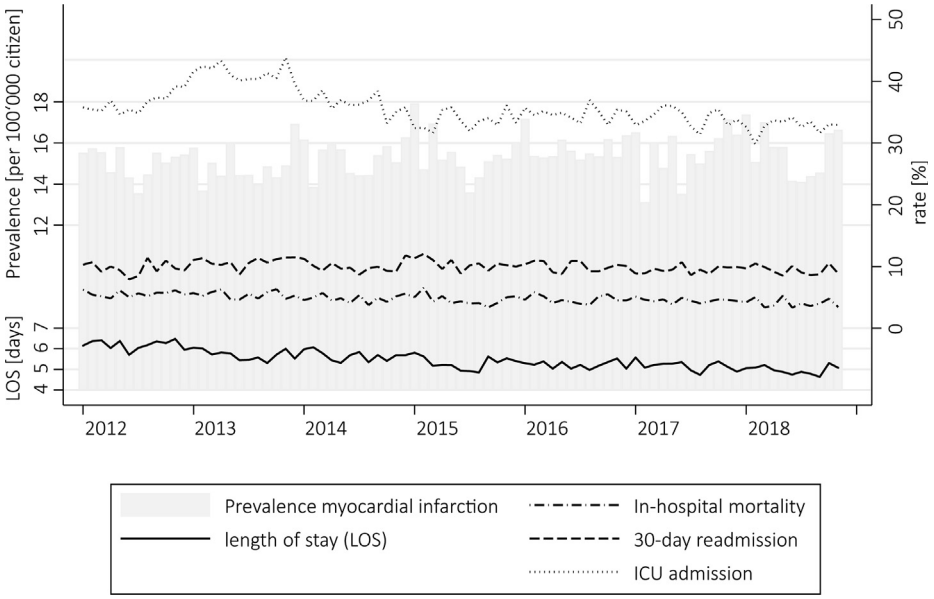

Fig. 1. Timetrend - Prevalence, in-hosp-mortality, ICU admission, length of stay and 30d readmission.

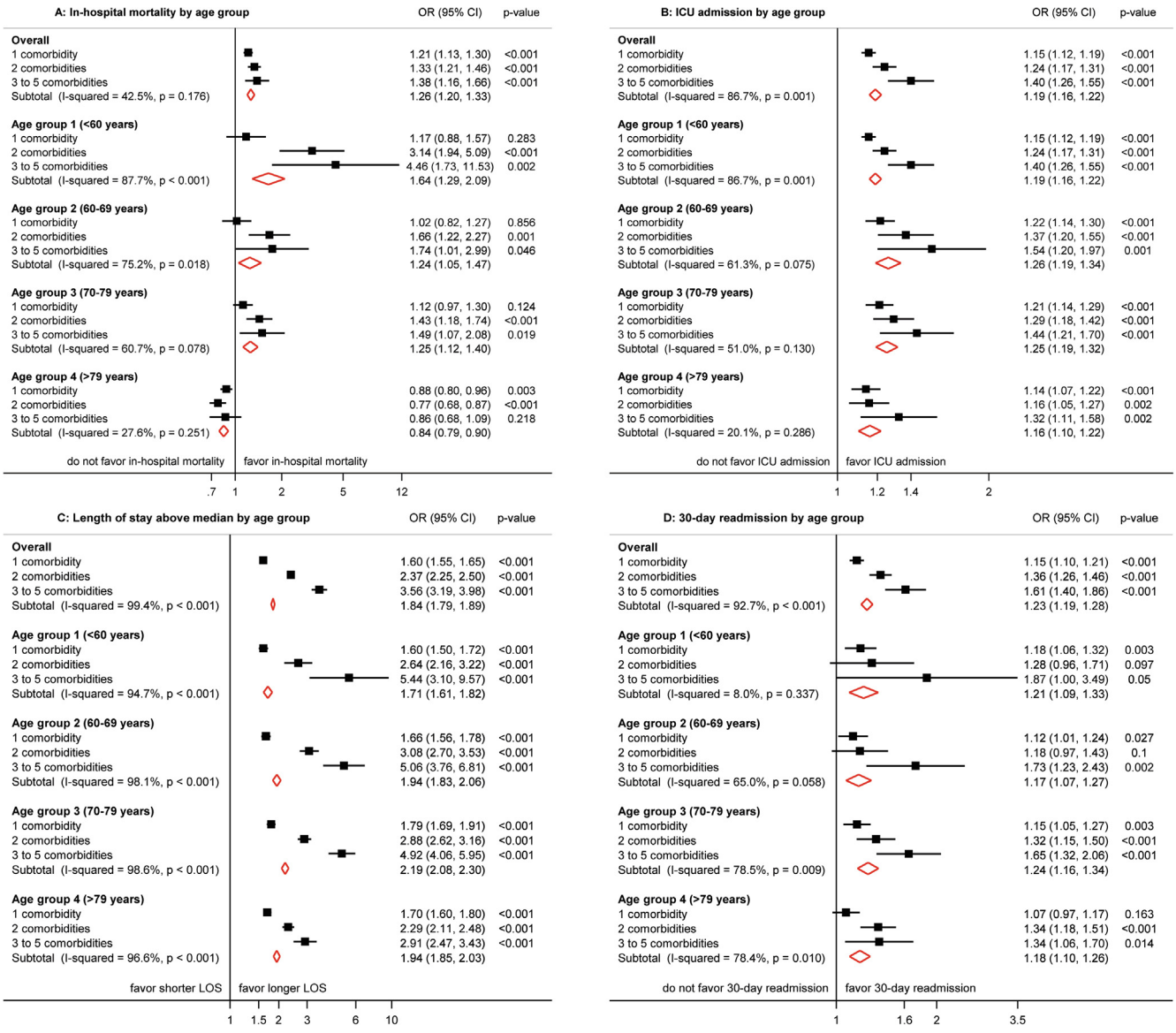

Fig. 2. (A) In-hospital mortality by age group, (B) ICU admission by age group, (C) Length of stay above median by age group, (D) 30-day readmission by age group.

3.3. In-hospital mortality

Stratifying by age-groups, we found an increase in in-hospital mortality from 1.1% in the youngest to 12.0% in the oldest patient group.

The stratified multivariable regression models show a stepwise increase in the odds of in-hospital mortality for each additional comorbidity among patients with an AMI (Fig. 2**A**). Overall, comorbid patients carried a similar excess risk in in-hospital mortality, independent of the numbers of prevalent comorbidities. However, while there was no difference in excess risk by increasing numbers of comorbidities in the oldest population, we observed an incremental risk by additional numbers of comorbidities in the youngest population. In the youngest age group, the overall risk for in-hospital mortality raised more than 60% (OR 1.64, 95% CI 1.29 to 2.09) among patients with any underlying comorbidity of interest, ranging from an OR of 1.17 in patients with one comorbidity of interest to an OR of 4.46 in patients with 3 or more comorbidities. This stepwise incremental risk for in-hospital mortality was strongest in younger patients and lost significance in older age groups. In the oldest population the risk for in-hospital mortality was even lower in comorbid patients compared to patients without a comorbidity of interest (OR 0.84, 95% CI 0.79 to 0.90).

CVD was the strongest predictor for in-hospital mortality (OR 2.24, 95% CI 1.95 to 2.57) with a stronger association in the younger age-groups (Fig. 3**A**).

In the oldest age group, the prevalence of DM, CKD, and PAD was protectively associated with in-hospital mortality (Fig. 3**A**).

3.4. Secondary outcomes

The results show a continuous increase in ICU admission rates with each additional comorbidity. Again, this relative effect was stronger in younger than in older patients. With an overall increased risk of 1.40 (95% CI 1.26 to 1.55) in patients with three or more comorbidities, the excessed risk for ICU admission was similar between the four age groups (Fig. 2**B**). The overall average LOS was 5.5 days (SD 6.0 days). The median LOS was 4 days and raised from 3 days among the youngest patients to 6 days in the oldest ones.

The risk for a prolonged LOS also showed a stepwise increase with each additional comorbidity and again, this increase was

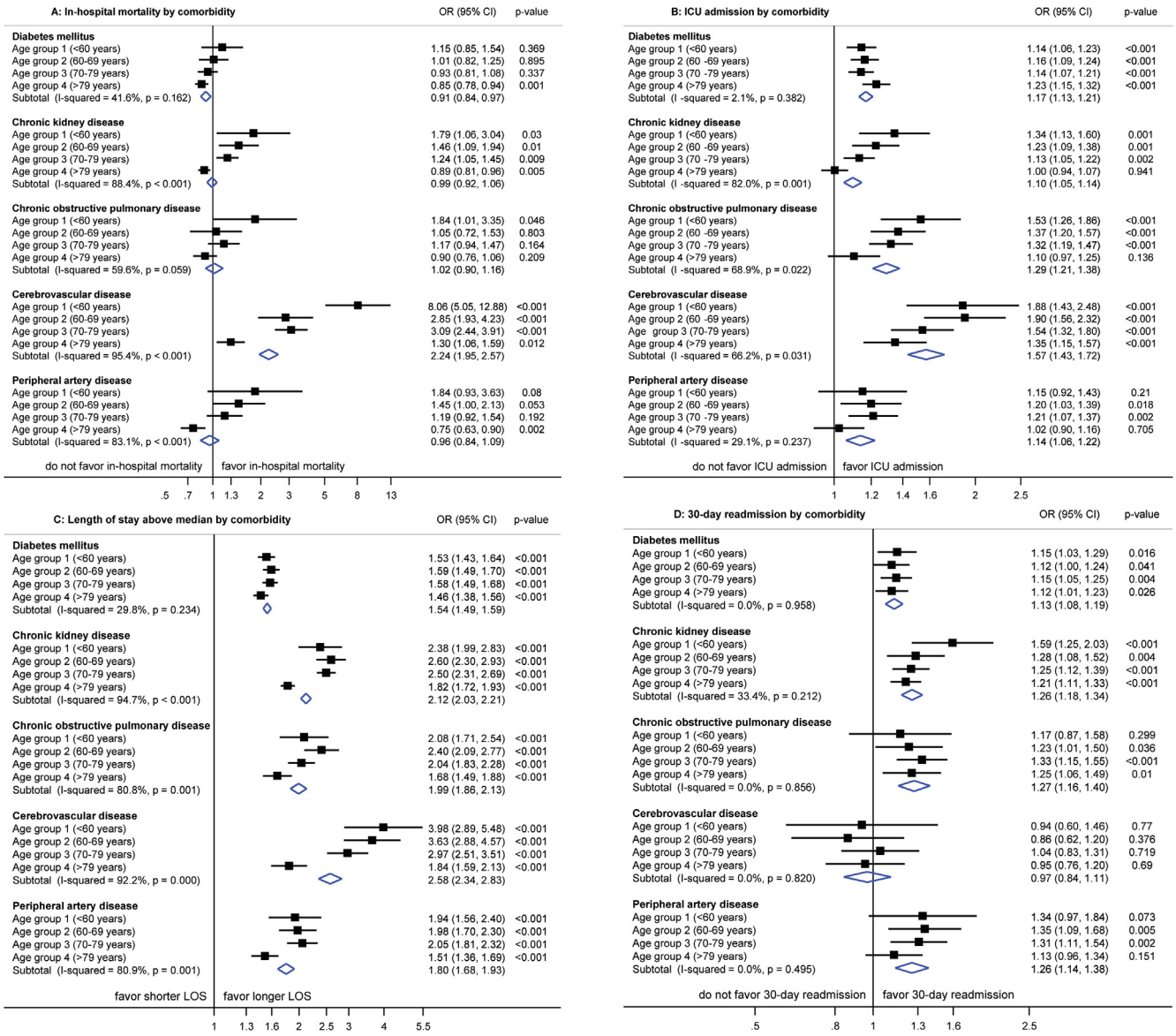

Fig. 3. (A) In-hospital mortality by comorbidity, (B) ICU admission by comorbidity, (C) Length of stay above median by comorbidity, (D) 30-day readmission by comorbidity.

much stronger in younger patients (OR 1.94, 95% CI 1.85 to 2.03) as compared to older patients (OR 1.71, 95% CI 1.61 to 1.82). While in youngest multimorbid patients with more than 2 comorbidities the risk for a prolonged LOS was more than five times elevated (OR 5.44, 95% CI 3.10 to 9.57) as compared with youngest patients without a comorbidity of interest, the excess risk was nearly three-fold among the oldest patients (OR 2.91, 95% CI 2.47 to 3.43). CVD was the strongest predictor for a prolonged hospitalization (OR 2.58, 95% CI 2.34 to 2.83) with the weakest association in older patients. This association was attenuated in patients with DM, CKD, COPD, and PAD (Figs. 2**C and** 3**C**).

Overall, 30-day readmission rates were comparable between the four age groups (Table 1, Fig. 2**D**). While the excess risk increased with each additional comorbidity in all age groups, we did not find an altered age dependent association.

DM, CKD, COPD, and PAD were all associated with increased 30-day readmission rates, but there was no age dependency (Fig. 3**D**).

4. Discussion

Key findings of this large study using a comprehensive set of administrative data of adult patients admitted for AMI are three-fold. First, we found an increase in prevalence of myocardial infarctions (e.g. NSTEMI) across the 7-year study period. Second, we observed a stepwise increase – mainly in younger patients - in risk for in-hospital mortality, ICU admission, prolonged LOS, and 30-day readmission with increasing number of comorbidities. The incremental risk of adverse patient outcomes was less pronounced in older patients. Third, the presence of CVD was the strongest effect modifier among age-groups investigating the excess risk of in-hospital mortality.

In line with previous studies, the number of patients admitted for AMI significantly increased during the study period [16]. However, as the incidence for STEMI remained stable, we may argue that this increase in NSTEMI is mainly caused by the diagnostic

use of more sensitive Troponin-assays which have been introduced since 2010 [17,18].

It is known that age is one of the strongest risk predictors for adverse events and mortality [19]. However, the incremental risk among stratified age-groups, caused by the presence of well-known comorbidities, is scarcely explored. Using real-world data, we found that especially younger hospitalized patients had a significantly increased excess risk in presence of comorbidities as compared with age-matched controls without underlying comorbidities of interest.

Earlier studies have explored the association of prevalent comorbidities and patient outcomes among admitted patients for AMI [20,21]. In summary, these studies found an increased risk of adverse outcomes in patients with multiple cardiac comorbidities. Further studies have shown a higher risk for mortality in multimorbid AMI patients [13,21–23]. As our study has investigated the association of five common comorbid conditions in a nationwide cohort including more than 100'000 AMI patients over a 7-year period, it reveals robust findings for admitted AMI patients, important to take into account when treating these patients. Mechanistical reasons remain debatable, however, the observed excess risk of multimorbidity may be attributable to a less effective or more complex clinical management. Moreover, multimorbidity per se may confer a poorer prognosis. Hence, it is obvious that prevalent comorbidities (i.e. DM, CKD, COPD, PAD or CVD) should not be neglected while caring for the acute coronary disease.

Interestingly, younger patients seem to be affected even more than older ones. One possible explanation may be that the presence of comorbidities at a younger stage might be usually more acute and severe (faster dynamic of disease) as compared with older patients. Another explanation of this effect is the survivorship bias which describes the toughness and higher compliance of older patients with their multimorbidity who have survived the early ears of illness and reached a high age despite their illness. These patients have a more continuous monitoring through regular appointments with general practitioners or specialists. Another reason for this large discrepancy between the age-groups might be the significant higher baseline risk for adverse outcomes in older patients. Therefore, it remains to be proven whether younger patients admitted for an AMI may profit from an intensified multimodal care.

Studies show that patients with CKD have an increased risk profile and poorer in-hospital results with a stronger effect in older patients [24,25]. Finally, our analysis supports this combined effect for in-hospital mortality, ICU admission rate, and 30-day readmission rate, but also implies that CKD, COPD and PAD have such a strong association on the LOS that patient age plays a much less significant role. Therefore, it was most likely more the comorbidity than the patient age which influenced the LOS in our population and we had no significant effect between the four age-groups [26].

DM seems to play a protective role in patients older than 80 years and reduces their in-hospital mortality significantly. We suspect that older patients suffering from DM are well controlled at a regular basis and therefore have a higher chance to be diagnosed with a more sub-clinical and less fatal myocardial event. Also, critically ill patients commonly suffer from stress-induced hyperglycemia which is known to be associated with mortality [27]. Patients with diabetes are less affected by high glucose levels than patients without diabetes [28–31].

5. Limitations

Our observational study has notable limitations. First, the retrospective design of our study does not allow causal conclusions. Second, we used administrative data with a lack of information about cardiovascular risk factors like smoking status, cardiovascular biomarkers (e.g. lipids, HbA1c), obesity or medication. Therefore, adjusting by these variables was not feasible. Third, administrative data brings the risk of misclassification of diseases. Fourth, we had no data about patient history, clinical appearance and laboratory parameter that plays an important role in the outcome of patients with AMI.

6. Conclusions

Among patients with acute myocardial infarction, we found a stepwise increase in risk for adverse clinical outcome with each additional comorbidity. This association was less obvious in older ones. If younger multimorbid patients suffering an AMI may benefit from an additional multimodal treatment to reduce their incremental risk of in-hospital mortality and other clinical outcomes still remains speculative and requires further prospective studies.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Kutz, D. Koch, A. Conca, C. Baechli, S. Haubitz, K. Regez, et al., Integrative hospital treatment in older patients to benchmark and improve outcome and length of stay – the In-HospiTOOL study, BMC Health Serv Res. 19 (2019) 237.
[2] K. Barnett, S.W. Mercer, M. Norbury, G. Watt, S. Wyke, B. Guthrie, Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study, Lancet 380 (2012) 37–43.
[3] A.K. Parekh, M.B. Barton, The challenge of multiple comorbidity for the US health care system, JAMA 303 (2010) 1303–1304.
[4] C.E. Aubert, J.L. Schnipper, N. Fankhauser, P. Marques-Vidal, J. Stirnemann, A.D. Auerbach, et al., Patterns of multimorbidity associated with 30-day readmission: a multinational study, BMC Public Health. 19 (2019) 738.
[5] F.T.T. Lai, S.Y.S. Wong, B.H.K. Yip, B. Guthrie, S.W. Mercer, R.Y. Chung, et al., Multimorbidity in middle age predicts more subsequent hospital admissions than in older age: a nine-year retrospective cohort study of 121,188 discharged in-patients, Eur. J. Int. Med. 61 (2019) 103–111.
[6] K.P. Alexander, M.T. Roe, A.Y. Chen, B.L. Lytle, C.V. Pollack Jr., J.M. Foody, et al., Evolution in cardiovascular care for elderly patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative, J Am. Coll Cardiol. 46 (2005) 1479–1487.
[7] A. Gruneir, S.E. Bronskill, C.J. Maxwell, Y.Q. Bai, A.J. Kone, K. Thavorn, et al., The association between multimorbidity and hospitalization is modified by individual demographics and physician continuity of care: a retrospective cohort study, BMC Health Serv. Res. 16 (2016) 154.
[8] R. Ofori-Asenso, E. Zomer, K.L. Chin, P. Markey, S. Si, Z. Ademi, et al., Prevalence and impact of non-cardiovascular comorbidities among older adults hospitalized for non-ST segment elevation acute coronary syndrome, Cardiovasc. Diagn. Ther. 9 (2019) 250–261.
[9] Swiss DRG. Regeln und Definitionen zur Fallabrechnung unter SwissDRG. https://www.swissdrg.org/application/files/4714/8111/3146/160620_SwissDRG_Falldefinitionen_v5.pdf; Accessed September 1, 2019.
[10] R. Clare, L. Duan, D. Phan, N. Moore, M. Jorgensen, A. Ichiuji, et al., Characteristics and clinical outcomes of patients with spontaneous coronary artery dissection, J. Am. Heart Assoc. 8 (2019) e012570.
[11] G.D. Rubinfeld, N.R. Smilowitz, J.S. Berger, J.D. Newman, Association of thrombocytopenia, revascularization, and in-hospital outcomes in patients with acute myocardial infarction, Am. J. Med. (2019).
[12] P. Shang, G.G. Liu, X. Zheng, P.M. Ho, S. Hu, J. Li, et al., Association between medication adherence and 1-year major cardiovascular adverse events after acute myocardial infarction in China, J. Am. Heart Assoc. 8 (2019) e011793.

[13] M. Sachdev, J.L. Sun, A.A. Tsiatis, C.L. Nelson, D.B. Mark, J.G. Jollis, The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease, J. Am. Coll. Cardiol. 43 (2004) 576–582.
[14] C. Berlin, P. Juni, O. Endrich, M. Zwahlen, Revascularization treatment of emergency patients with acute st-segment elevation myocardial infarction in switzerland: results from a nationwide, cross-sectional study in Switzerland for 2010–2011, PLoS One. 11 (2016) e0153326.
[15] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J Chronic Dis. 40 (1987) 373–383.
[16] E. Puymirat, T. Simon, G. Cayla, Y. Cottin, M. Elbaz, P. Coste, et al., Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI program (French registry of acute ST-elevation or Non-ST-elevation myocardial infarction) 1995 to 2015, Circulation 136 (2017) 1908–1919.
[17] A.S. Shah, A. Anand, Y. Sandoval, K.K. Lee, S.W. Smith, P.D. Adamson, et al., High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study, Lancet 386 (2015) 2481–2488.
[18] R. Twerenbold, J. Boeddinghaus, T. Nestelberger, K. Wildi, M. Rubini Gimenez, P. Badertscher, et al., Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction, J. Am. Coll. Cardiol. 70 (2017) 996–1012.
[19] A. Loyeau, H. Benamer, S. Bataille, S. Tepper, T. Boche, L. Lamhaut, et al., Evolution of ST-elevation acute myocardial infarction prevalence by gender assessed age pyramid analysis-the piramyd study, J. Clin. Med. (2018;7.).
[20] H.Y. Chen, J.S. Saczynski, D.D. McManus, D. Lessard, J. Yarzebski, K.L. Lapane, et al., The impact of cardiac and noncardiac comorbidities on the short-term outcomes of patients hospitalized with acute myocardial infarction: a population-based perspective, Clin. Epidemiol. 5 (2013) 439–448.
[21] D.D. McManus, H.L. Nguyen, J.S. Saczynski, M. Tisminetzky, P. Bourell, R.J. Goldberg, Multiple cardiovascular comorbidities and acute myocardial infarction: temporal trends (1990–2007) and impact on death rates at 30 days and 1 year, Clin. Epidemiol. 4 (2012) 115–123.
[22] J. Sanchis, V. Ruiz, C. Bonanad, E. Valero, M.A. Ruescas-Nicolau, Y. Ezzatvar, et al., Prognostic value of geriatric conditions beyond age after acute coronary syndrome, Mayo Clinic Proceedings: Elsevier (2017) 934–939.
[23] J. Sanchis, M. Soler, J. Nunez, V. Ruiz, C. Bonanad, F. Formiga, et al., Comorbidity assessment for mortality risk stratification in elderly patients with acute coronary syndrome, Eur. J. Int. Med. 62 (2019) 48–53.
[24] E. Akkaya, E. Ayhan, H. Uyarel, M. Ergelen, A. Turer, D. Demirci, et al., The impact of chronic kidney disease on in-hospital clinical outcomes in patients undergoing primary percutaneous angioplasty for ST-segment elevation myocardial infarction, Turk Kardiyol Dern Ars. 39 (2011) 276–282.
[25] J.S. Choi, Y.A. Kim, Y.U. Kang, C.S. Kim, E.H. Bae, S.K. Ma, et al., Clinical impact of hospital-acquired anemia in association with acute kidney injury and chronic kidney disease in patients with acute myocardial infarction, PLoS One. 8 (2013) e75583.
[26] S. Kotwal, I. Ranasinghe, D. Brieger, P.A. Clayton, A. Cass, M. Gallagher, The influence of chronic kidney disease and age on revascularization rates and outcomes in acute myocardial infarction – a cohort study, Eur. Heart J. Acute Cardiovasc Care. 6 (2017) 291–298.
[27] Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clinic Proceedings: Elsevier; 2003. p. 1471-8.
[28] B.B. Graham, A. Keniston, O. Gajic, C.A.T. Alvarez, S. Medvedev, I.S. Douglas, Diabetes mellitus does not adversely affect outcomes from a critical illness, Crit. Care Med. 38 (2010) 16–24.
[29] M. Egi, R. Bellomo, E. Stachowski, C.J. French, G.K. Hart, C. Hegarty, et al., Blood glucose concentration and outcome of critical illness: the impact of diabetes, Crit. Care Med. 36 (2008) 2249–2255.
[30] M. Falciglia, R.W. Freyberg, P.L. Almenoff, D.A. D'Alessio, M.L. Render, Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis, Crit. Care Med. 37 (2009) 3001.
[31] S.E. Siegelaar, M. Hickmann, J.B. Hoekstra, F. Holleman, J.H. DeVries, The effect of diabetes on mortality in critically ill patients: a systematic review and meta-analysis, Crit Care. 15 (2011) R205.