Acute Heart Failure in the Young:

Clinical characteristics and biomarker profiles

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Conflict of interest

Dr. Cleland was on the Steering Committee for the PROTECT trial; served on the advisory board for MSD; and received payments for both. Dr. O'Connor is a consultant to Merck. Dr. Ponikowski has received honoraria from Merck; Dr. Davison and Dr. Cotter are employees of Momentum Research Inc, which was contracted to perform work on the study by Merck. Dr. Metra have received honoraria and reimbursements from NovaCardia, sponsors of the study, and Merck. Dr. Givertz has received institutional research support and served on a scientific Advisory Board for Merck. Dr. Teerlink has received research grants and consultation fees from: Amgen, Bayer, Cytokinetics, Medtronic, Merck, Novartis, St. Jude, Trevena.. Dr. Bloomfield is an employee of Merck. Dr Dittrich served as a consultant to Merck. Dr. Voors has received speaker and consultancy fees from Merck. All other authors have reported that they have no conflict of interest to declare and that they take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Key words: heart failure, age, young, biomarker

Abstract word count: 235 Text word count: 5448

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Abstract

Background: Young patients (<50 years) exhibit specific characteristics in chronic heart failure (HF), but their phenotype in acute heart failure (AHF) is not well described.

Methods and Results: 2033 patients of the PROTECT trial were divided into two groups: young patients (≤50 years) and older patients (>50 years). Biomarkers from different pathophysiological domains were available in 1266 patients. Patients were compared with regard to clinical characteristics, biomarker profiles, and in-hospital (worsening renal function [WRF] and decongestion) and post-discharge (180-day survival) outcome. Young patients (n=121) were mostly men, had fewer comorbidities with better renal function, and more often had a reduced ejection fraction. At admission, young patients were more likely to have jugular venous distension, but less rales and dyspnea compared with older patients. During hospitalization, young patients received higher loop diuretic doses, and were decongested earlier than older patients. WRF occurred less frequently in young patients (5.9% vs. 13.3%, p=0.020) and they were more often discharged alive. At 180 days, the mortality of young patients was lower than that of the older patients (9.9% vs. 18.1, p=0.021). Biomarker levels indicative of inflammation and renal damage were lower in the young, although they exhibited higher BNP levels than older patients.

Conclusions: Despite use of higher diuretic doses, young patients with AHF less often developed WRF during hospitalization and had better outcomes than older patients. Differences in biomarker levels between the age groups suggest distinct underlying pathophysiologies.

https://clinicaltrials.gov numbers NCT00328692 and NCT00354458

Introduction

The incidence of heart failure (HF) increases with age, and HF is a common disease of elderly patients[1,2]. Data on HF in patients aged less than 50 years are limited[1,3,4]. Three studies reported on the characteristics and clinical outcome of younger patients with chronic HF, which indicate a distinct phenotype, typically comprising non-ischemic etiology, more severe left ventricular dysfunction and less concomitant comorbidities compared to older patients[5–10].

Most studies in AHF focus on the elderly[3,4]. However, the specific characteristics and the clinical outcome of young patients who are hospitalized for acute HF (AHF) are currently not well described. Therefore, we sought to characterize differences in baseline characteristics, management, and clinical outcomes of young patients compared to older patients hospitalized for AHF. In addition, we studied biomarkers from different pathophysiological domains in young versus older patients to gain insight in underlying differences in pathophysiology.

Methods.

Study design and population

The Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion (PROTECT) was a multicenter, randomized, placebo-controlled trial for which the design and primary results have previously been published[11–13]. In brief, PROTECT included 2033 patients hospitalized for AHF with impaired renal function (estimated creatinine clearance between 20 and 80ml/min), signs and symptoms of fluid overload, concomitant dyspnea, NYHA III–IV symptoms, systolic blood pressure

≥ 95mmHg, who required i.v. diuretic therapy. Overall results of the PROTECT trial were neutral and have been previously reported[11,13]. This study complied with the Declaration of Helsinki and was approved by local Ethics Committees. All patients provided written informed consent.

Definitions and endpoints

Patients younger than or equal to 50 years were classified as “young”; whereas the remainder of patients was referred to as older (>50 years) in accordance with previous publications [3,5]. HF with preserved ejection fraction (HFpEF) was defined as left ventricular ejection fraction (LVEF) >45% based on available echocardiographic data in 976 patients. The total diuretic dose through day 4 was defined as the sum of the daily oral (p.o.) and intravenous (i.v.) diuretic doses, weighing the effects of i.v. loop diuretics with the factor 1 and those of p.o. loop diuretics with the factor 0.5.

The primary and secondary endpoints of PROTECT have previously been described in detail[11,12]. We assessed the primary pre-specified trichotomous endpoint, a classification of therapy response into ‘‘success’’ (Improvement in dyspnea (7-point Likert scale) without treatment failure), ‘‘failure’’ (Death or readmission for heart failure to day 7, worsening heart failure symptoms from >1 to 7 days after treatment, requiring rescue therapy, or persistent renal impairment) or ‘‘unchanged’’ across age groups. Additionally, the secondary end points 60-day death and hospitalizations, 60-day death or rehospitalization, 60-day death or HF rehospitalization, 60-day HF rehospitalization, 60-day death, cardiovascular or renal rehospitalization and 180-day mortality were analyzed. An independent endpoint committee adjudicated all rehospitalizations through day 60 and deaths through day 180.

Biomarkers

Of the 2033 patients in PROTECT, 1266 patients had complete biomarker data available at baseline. Forty-eight biomarkers were assessed for the present analysis. Blood urea nitrogen (BUN) and creatinine, were measured in a central laboratory (ICON Laboratories, Farmingdale, New York). A panel of 26 biomarkers was measured by Alere Inc., San Diego, CA, USA. Galectin-3, myeloperoxidase and neutrophil gelatinase-associated lipocalin (NGAL) were measured using sandwich enzyme-linked immonsorbent assays (ELISA) on a microtiter plate; angiogenin and C-reactive protein (CRP) were measured using competitive ELISAs on a Luminex® platform; D-dimer, endothelial cell-selective adhesion molecule, growth differentiation factor 15 (GDF-15), lymphotoxin beta receptor, mesothelin, neuropilin, N-terminal pro C-type natriuretic peptide (NT-proCNP), osteopontin, procalcitonin, pentraxin-3, periostin, polymeric immunoglobulin receptor, pro-adrenomedullin (proADM), prosaposin B, receptor for advanced glycationendproducts, soluble ST-2 (sST-2), syndecan-1, tumor necrosis factor alpha receptor 1 (TNFR-1), Troy, vascular endothelial growth receptor 1 (VEGFR-1) and WAP four-disulphide core domain protein HE4 were measured using sandwich ELISAs on a Luminex® platform. Immunoassays to PCT, proADM, Galectin-3 and ST2 were developed by Alere. These research assays have not been standardized to the commercialized assays used in research or in clinical use and the extent to which each Alere assay correlates with the commercial assay is not fully characterized (supplementary table 1).

Additionally, a panel of four biomarkers – Endothelin-1 (ET-1), Interleukin-6 (IL-6), Kidney Injury Molecule 1 (KIM-1) and cardiac specific Troponin I (cTnI) was measured in frozen plasma samples collected at baseline using high sensitive single

molecule counting (SMC™) technology (RUO, Erenna® Immunoassay System, Singulex Inc., Alameda, CA, USA) (see supplementary methods for details). N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured during screening using commercial assays available at the study centers or a point of care device provided to study sites when needed.

Statistical analyses

Summary baseline statistics for continuous variables are presented as mean with standard deviation or median with interquartile range as appropriate, and proportions for categorical variables.

Equality of the means of continuous, normally distributed variables across age groups were tested using Students' t-test. Equality of ranks of continuous, skewed distributed variables across age groups were tested using the Mann-Whitney-U test. Independent distributions of frequencies in categorical variables between age groups were tested using Pearson's chi-squared test.

Statistical analyses were performed using STATA (version 13.1. STATA Corp. College Station. TX. USA). Two-sided P-values < 0.05 were considered statistically significant.

Results

Baseline characteristics.

Table 1 shows the baseline demographic and clinical characteristics in both age groups.

A total of 121 (6%) patients in PROTECT were younger than 50 years, with a mean age of 43.9±6.4 years. Young patients were predominantly men, had a higher body mass index and higher estimated glomerular filtration rate, while having lower

left ventricular ejection fraction, lower systolic blood pressure and higher heart rate compared to older patients. They had lower rates of ischemic heart disease, atrial fibrillation, hypertension, stroke and peripheral vascular disease. However, the proportion of patients with a history of HF and hospitalization for HF during the previous year was higher in young patients.

Details on medication, non-pharmacological therapy and treatment response during hospitalization are presented in *table 2* and *figure 1*. Younger patients were more often treated with beta-blockers and mineral receptor antagonists, and less often with nitrates and calcium channel blockers. Additionally, mineral receptor antagonists were more often initiated and/or their doses were more often increased in young patients during hospitalization (*figure 1)*.

Outcomes

Young patients were treated with higher IV and oral loop diuretic doses during hospitalization (*table 2)* than older patients. From admission to day 4, young patients showed the higher absolute weight loss, while diuretic response was similar compared to the older patients. Additionally, young HF patients showed lower rates of worsening renal function (WRF) (5.8% vs. 15.3%, p=0.004) (*table 2*).

The primary pre-specified trichotomous endpoint did not differ across the age groups, albeit that young AHF patients were more frequently readmitted for HF, but less often showed serum creatinine increase and persistent renal impairment (*table 3*). Young patients had lower 180-day mortality (9.9% vs. 18.1%, p=0.021) (*table 3*). HF / pump failure was the most frequent cause of death in young patients (*table 3)*.

Biomarker profiles

The levels of biomarkers at baseline are shown in *table 4*. Younger patients had lower levels of IL-6, PIGR, TNFR1A, WAP4C, galectin 3, mesothelin, LTBR, ESAM-1, BUN, NGAL and KIM-1. In contrast, VEGFR1 and angiogenin were higher in young patients.

Discussion

This study provides a comprehensive overview of clinical characteristics, in-hospital management, clinical outcomes and biomarker differences between young and older AHF patients. Young patients had distinct signs and symptoms of acute HF at hospital admission compared to the elderly. Furthermore, during hospitalization young patients were treated with higher diuretic doses, which led to a similar diuretic response. However, diuretic treatment was accompanied by less WRF during hospitalization. Biomarker levels significantly differed between both age groups. Compared to older patients, the young AHF patients mainly exhibited lower levels of biomarkers indicative of inflammation and renal damage.

Overall, young patients showed a typical pattern of signs and symptoms of AHF at admission, which confirms previous reports in a chronic setting [5,6]. They less frequently had rales, dyspnea and angina, but a higher jugular venous pressure. Young patients with AHF had a more favorable clinical profile with less comorbidities, less ischemic etiology and less renal dysfunction than older patients, as previously reported in patients with chronic heart failure[5]. Although several other studies explored the clinical features of acute heart failure and their relationship with patient age, these studies primarily focused on the characteristics of elderly patients, rarely included patients younger than 50 years of age and are limited to only few standard blood biomarkers [4,7,14]. Importantly, Metra et al. previously analyzed the influence of age on patient characteristics and outcome. He found that with increasing age, patients more often exhibited characteristics such as female sex, hypertension, atrial fibrillation, and higher left ventricular ejection fraction. This was paralleled by independent increased risk of adverse 30- and 180-day outcomes [4].

In our study, young patients had higher estimated glomerular filtration rates at admission, and during hospitalization for AHF they experienced less persistent WRF. The less impaired renal function at baseline is typical for younger compared to older patients with acute heart failure and could in part explain that during diuretic therapy, young patients less frequently developed WRF than older HF patients [15]. Young HF patients were treated with higher doses of diuretics and showed more weight loss. Interestingly, a recent sub-analysis of the EVEREST trial showed that a worse congestion status during AHF hospitalization was associated with worse outcomes[16]. The data from this study suggest that the better diuretic response of the young patients in our study is related to a better renal function, which translates to more favorable outcomes with regard to the primary endpoint.

We used biomarkers to better characterize acute heart failure in the young. Overall, young patients had lower levels of inflammatory markers. There is a clear pattern of lower median values of inflammatory biomarkers in the younger patients as opposed to older patients, although only few biomarkers, such as IL-6, TNFR1A, LTBR and WAP4C, reached the statistical significance level. The lower level of inflammation can potentially be explained by the fact that younger patients suffer from less comorbidities and more often had HFrEF[17–19]. It has been hypothesized that comorbidities, such as COPD and aging, contribute to a general pro-inflammatory state, which is accompanied by higher levels of inflammation markers and more prevalent in the elderly[20,21]. This also holds true for our data, where young AHF patients had more HFrEF and fewer comorbidities compared to their elder peers. Notably, this effect can be detected despite the higher body mass index in the younger patients. Although it is known that obesity should actually be associated with an increase in biomarkers of inflammation, our study shows that the

level of inflammation in younger patients with acute decompensated heart failure is lower than that of older patients.

Furthermore, biomarkers associated with poor renal function (BUN, NGAL, KIM-1, galectin-3) were lower in younger patients[22–26]. This correlates with the finding that younger patients overall had a better renal function at admission and were less often subject to WRF during hospitalization.

Angiogenesis markers had a heterogeneous distribution across both age groups. Levels of endothelial cell-selective adhesion molecule (esam-1), an endothelial dysfunction marker, were found to be lower in the young; this likely reflects that the young less often had a history of myocardial infarction and ischemic heart disease[27]. Indeed, higher levels of esam-1 were previously found to be associated with arteriosclerosis[27]. Additionally, higher esam-1 levels were shown to be independently associated with impaired renal function[28]. Furthermore, mesothelin levels were previously found to be higher in patients with impaired renal function, which is in accordance with our results[29]. Angiogenin and VEGFR1, which had the highest levels in young patients, were linked to angiogenesis and revascularization[30–33]. Both markers are pathophysiologically involved in vascular repair and cardiac remodeling, both of which are etiological factors for the development of HFrEF. Angiogenesis is impaired in the elderly, possibly also contributing to the lower levels of these two biomarkers in the older patients[33].

The main clinical implication of our findings is that younger patients with AHF are a distinct subgroup. Young patients can be decongested more aggressively at lower risk of worsening renal function with anticipated better outcomes than older patients with AHF. Biomarkers reflect a characteristic pattern of pathophysiological processes in young patients.

Limitations

A limitation of our study is the relatively small sample size of patients' younger than 50 years of age and the misbalance compared to the much larger group of older patients, which could introduce bias to the detected differences. Additionally, as a *post hoc* study, a possible selection bias may be present. Lastly, the main PROTECT trial was not primarily designed to assess mortality.

Conclusions.

Despite being treated with higher dosage of diuretic therapy, young AHF patients develop less WRF compared to their older peers during hospitalization. Clinically, young AHF patients in the PROTECT dataset had lower LVEFs, fewer comorbidities and a lower rate of HFpEF. Biomarkers potentially reflect these pathophysiological differences between young and older AHF patients.

Acknowledgements

None

Funding Sources

Disclosures

None

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Figure Legends

Figure 1: Stacked bar charts showing medication dose changes for ace-inhibitors, beta blockers and mineral receptor inhibitors.

Table 1. Baseline differences of clinical characteristics across age groups

	≤50	**>50**	**p-value**
N	121 (6%)	1912 (94%)	
Demographics			
Age, years, mean ± SD	43.9 ± 6.4	71.8 ± 9.6	**<0.001**
Male sex, (%)	83.5	66.1	**<0.001**
BMI, kg/m2, mean ± SD	31.0 ± 9.3	28.7 ± 5.9	**<0.001**
eGFR, mL/min/1.73 m2, mean ± SD	63.2 ± 24.8	47.6 ± 18.6	**<0.001**
NYHA class, (%)			0.470
I/II	15.7	18.0	
III	56.5	50.7	
IV	27.8	31.3	
LVEF,%, median (IQR)	25 (20, 35)	30 (23, 40)	**<0.001**
HFpEF (EF >45), (%)	7.0	16.4	**0.038**
Systolic BP, mmHg, mean ± SD	116.2 ± 16.6	124.8 ± 17.6	**<0.001**
Diastolic BP, mmHg, mean ± SD	74.3 ± 12.4	73.7 ± 11.8	0.580

Heart rate, b.p.m. mean ± SD	84.9 ± 14.0	79.8 ± 15.5	**<0.001**
Medical history			
Mitral regurgitation, (%)	38.8	33.6	0.230
Heart failure (HF), (%)	95.0	94.8	0.900
Hospitalization for HF previous year,(%)	63.6	48.4	**0.001**
HF hospitalizations, median (IQR)	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	**0.043**
Ischemic heart disease, (%)	30.6	72.3	**<0.001**
Myocardial infarction, (%)	25.6	50.8	**<0.001**
Hypertension, (%)	63.6	80.4	**<0.001**
Stroke or PVD, (%)	7.4	19.0	**0.001**
COPD or asthma, (%)	14.0	20.2	0.100
Diabetes mellitus, (%)	29.2	46.4	**<0.001**
History of Atrial Fibrillation/Flutter, (%)	28.3	56.3	**<0.001**
AICD, (%)	29.8	15.1	**<0.001**
Pacemaker, (%)	6.7	12.6	0.054
Medication prior to admission, (%)			
Beta-blockers, (%)	86.0	75.6	**0.010**
ACE-I/ARB, (%)	79.3	75.4	0.330

MRA, (%)	58.7	42.8	**<0.001**
Digoxin, (%)	28.1	28.1	0.990
Nitrates, (%)	10.7	26.9	**<0.001**
CCBs, (%)	4.1	14.2	**0.002**
Presenting signs & symptoms			
Orthopnea, (%)	81.9	83.9	0.580
Dyspnea at rest (NYHA IV), (%)	47.4	57.6	**0.031**
Angina pectoris, (%)	8.3	22.9	**<0.001**
Edema, (%)	24.8	27.8	0.470
JVP, (%)	51.9	39.9	**0.014**
Rales, (%)	4.1	10.2	**0.030**

Abbreviations: ACEI: Angiotensin converting enzyme inhibitor, ARB: aldosterone receptor blocker, BMI: body mass index, BP: blood pressure, CCB: calcium channel blocker, COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, HFpEF: heart failure with a preserved ejection fraction, MRA: mineral receptor antagonist, NYHA: New York heart association, PVD: peripheral vascular disease

Table 2. Treatment characteristics during hospitalization

	≤50 yrs	>50 yrs	p-value
N	121	1912	
Diuretics & diuretic response			
IV loop diuretic dose (mg)			
Day 2, median (IQR)	80.0 (40.0, 175.0)	80.0 (40.0, 140.0)	0.360
Day 3, median (IQR)	80.0 (40.0, 190.0)	76.8 (40.0, 120.0)	**0.024**
Day 4, median (IQR)	63.8 (0.0, 120.0)	40.0 (0.0, 100.0)	**0.019**
Total diuretic dose (mg)			
through Day 2, median (IQR)	170.0 (100.0, 260.0)	220.0 (160.0, 360.0)	0.110
through Day 3, median (IQR)	267.5 (150.0, 350.0)	355.0 (240.0, 546.3)	0.260
through Day 4, median (IQR)	220.0 (200.0, 420.0)	450.0 (320.0, 720.0)	0.065
Total IV diuretics (mg)			
through Day 2, median (IQR)	200.0 (100.0, 400.0)	160.0 (120.0, 300.0)	**0.036**
through Day 3, median (IQR)	340.0 (200.0, 610.0)	260.0 (179.7, 480.0)	**0.005**
Total loop diuretics (mg) Day 7 or discharge, median (IQR)	320.0 (120.0, 780.0)	280.0 (130.0, 560.0)	0.160
Weight (kg)			

Day1, mean ± SD	93.3 ± 29.5	81.2 ± 18.5	**<0.001**
Day4, mean ± SD	89.1 ± 27.9	78.3 ± 17.7	**<0.001**
Δweight (kg)			
Day1 to 2, mean ± SD	-1.5 ± 2.4	-1.4 ± 1.9	0.600
Day1 to 3, mean ± SD	-2.7 ± 3.0	-2.3 ± 2.5	0.051
Day1 to 4, mean ± SD	-3.4 ± 3.8	-2.8 ± 2.9	**0.048**
Diuretic response (kg)			
Day2, mean ± SD	-0.8 ± 0.9	-0.7 ± 0.9	0.420
Day3, mean ± SD	-0.6 ± 0.6	-0.5 ± 0.7	0.600
Day4, mean ± SD	-0.5 ± 0.5	-0.4 ± 0.5	0.640
Patients without diuretic response, %	25.0	18.7	0.750
IV Diuretic response (kg)			
Day2, mean ± SD	-0.9 ± 1.2	-0.9 ± 1.4	0.270
Day3, mean ± SD	-0.8 ± 0.8	-0.6 ± 0.9	0.130
Day4, mean ± SD	-0.6 ± 0.8	-0.5 ± 0.7	0.450
In-hospital outcome			
Worsening renal function, %	5.8	15.3	**0.004**
Discharged alive, %	98.3	95.5	0.130

Days of Initial Hospital Stay, median (IQR)	7.0 (5.0, 13.0)	8.0 (6.0, 14.0)	0.140

Table 3. Individual components of the primary endpoint, rehospitalization details and mode of death

	≤50 (n=121)	**>50 (n=1912)**	**p-value**
Primary endpoint			0.100
Treatment success*, %	47.1	38.6	
Patient unchanged†, %	38.0	39.9	
Treatment failure (any 1 of the following) through day 7, %	14.9	21.5	
Death‡, %	0.0	1.9	0.120
Readmission for heart failure, %	2.5	0.3	**<0.001**
In-hospital worsening heart failure§, %	9.1	9.5	0.890
Persistent renal impairment| |, %	5.9	13.3	**0.020**
Serum creatinine increase of ≥0.3 mg/dL, %	5.9	12.9	**0.027**
Hemofiltration or dialysis, %	0.8	0.6	0.730
Rehospitalization through Day 60			
Frequency, median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.390
Days, mean ± SD	3.2 ± 7.4	2.7 ± 6.1	0.400
Days alive and out of hospital, mean ± SD	44.4 ± 15.3	42.4 ± 16.5	0.200
Rehospitalization or death, %	33.9	33.2	0.880

Rehospitalization (cardiovascular or renal) or death, %	28.9	28.6	0.940
Rehospitalization (heart failure) or death, %	23.1	21.5	0.670
Death through Day 180			
Death, %	9.9	18.1	**0.021**
Causes of death			0.450
Heart failure / pump failure, %	66.7	51.6	
Sudden death, %	0.0	12.1	
Cardiac (no-heart failure), %	0.0	7.4	
Vascular, %	0.0	8.4	
Sepsis/pneumonia, %	0.0	8.4	
Other non-cardiovascular, %	16.7	8.9	
Unknown, %	16.7	3.2	

Table Legend:

*, Treatment success (determined at 24 and 48 hours after the start of study drug [Day 2 and 3] or the day of discharge, if earlier):
Dyspnea reported by the patient using a 7-point Likert scale as moderately or markedly better compared with study start, AND Not a treatment failure
†, Patient unchanged: Neither treatment success nor treatment failure
‡, Death or readmission for heart failure any time through Day 7
§, Worsening symptoms and/or signs of heart failure occurring >24 hours after the start of study drug to Day 7 or discharge, whichever occurs first, such that there is a need for any one of the following types of ‘‘rescue therapy’’: an increase in the dose or reinstitution of IV loop diuretic therapy, or initiation of oral metolazone or IV chlorothiazide as accompanying therapy to loop diuretics initiation of ultrafiltration initiation of IV positive inotropes, vasopressors, or IV vasodilators initiation of mechanical ventilatory (including BiPAP or CPAP) or circulatory support
| |, Persistent renal impairment as defined by a serum creatinine increase of ≥0.3 mg/dL (25.5 umol/L) from randomization to Day 7, confirmed at Day 14, or the initiation of hemofiltration or dialysis through Day 7

Table 4. Baseline biomarkers across age groups

Age (years)	**≤50 yrs**	**>50 yrs**	**p-value**
N	121	1912	
Inflammation			
CRP (ng/ml)	13.0 (8.5, 25.1)	14.1 (7.4, 27.9)	0.910
D-Dimer (ng/ml)	152.5 (90.6, 273.1)	163.3 (90.6, 355.8)	0.180
GDF-15 (ng/ml)	4.6 (2.6, 6.3)	4.5 (3.1, 6.3)	0.510
Interleukin 6 (pg/ml)	9.4 (5.2, 14.7)	11.2 (6.6, 21.2)	**0.029**
Pentraxin-3 (ng/ml)	3.9 (2.6, 6.9)	4.4 (2.9, 7.0)	0.230
Procalcitonin (ng/ml)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.520
PIGR (ng/ml)	280.8 (204.4, 391.7)	405.8 (266.4, 671.9)	**<0.001**
PSAP-B (ng/ml)	35.9 (26.8, 51.0)	38.6 (28.5, 53.6)	0.100
RAGE (ng/ml)	4.8 (3.6, 7.2)	5.0 (3.6, 6.7)	0.900
TNF-R1a (ng/ml)	2.3 (1.7, 3.5)	3.3 (2.3, 4.8)	**<0.001**
WAP4C (ng/ml)	17.4 (8.7, 31.0)	28.4 (14.8, 52.9)	**<0.001**
Oxidative stress			
MPO (ng/ml)	37.4 (16.4, 67.4)	34.0 (18.3, 71.1)	0.990
Remodeling			

Syndecan-1 (ng/ml)	8.3 (6.9, 10.1)	8.4 (7.0, 10.1)	0.510
Periostin (ng/ml)	6.3 (3.3, 9.8)	5.5 (3.2, 8.9)	0.310
Galectin-3 (ng/ml)	30.1 (25.3, 44.2)	36.5 (27.9, 49.0)	**0.003**
Osteopontin (ng/ml)	109.3 (73.9, 155.3)	112.3 (78.5, 168.1)	0.450
Cardiac Stretch			
BNP (pg/ml)	522.8 (348.2, 930.2)	441.7 (253.8, 796.9)	0.050
ST-2 (ng/ml)	4.5 (1.6, 8.0)	3.5 (1.0, 8.0)	0.210
Troponin I (pg/ml)	7.4 (4.6, 14.5)	10.7 (5.6, 23.5)	**0.004**
Angiogenesis			
VEGFR (ng/ml)	0.5 (0.3, 0.8)	0.4 (0.2, 0.6)	**<0.001**
Angiogenin (ng/ml)	2299.5 (1451.5, 3117.1)	1833.0 (1232.0, 2761.3)	**0.030**
Mesothelin (ng/ml)	80.5 (68.5, 92.3)	87.2 (74.7, 101.3)	**0.001**
Neuropilin (ng/ml)	12.9 (9.1, 19.2)	12.5 (8.2, 17.5)	0.370
proADM (ng/ml)	2.7 (1.6, 4.6)	2.8 (1.5, 4.8)	0.730
NTpro-CNP (ng/ml)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	**0.036**
Endothelin 1 (pg/ml)	7.2 (5.4, 9.6)	6.8 (4.9, 9.2)	0.140
Troy (ng/ml)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	**<0.001**
Arteriosclerosis			

ESAM (ng/ml)	59.5 (55.6, 63.8)	62.2 (56.4, 69.8)	**0.002**
LTBR (ng/ml)	0.3 (0.2, 0.5)	0.4 (0.3, 0.6)	**<0.001**
Renal function			
NGAL (ng/ml)	57.1 (39.8, 92.0)	83.9 (54.2, 137.6)	**<0.001**
KIM 1 (pg/ml)	206.7 (108.0, 340.2)	299.5 (186.8, 489.6)	**<0.001**
BUN (mg/dl)	24.0 (19.0, 37.0)	30.0 (22.0, 41.0)	**<0.001**

Abbreviations: CRP: C-reactive protein, ESAM: endothelial cell-selective adhesion molecule, ET-1: endothelin-1, GDF-15: growth differentiation factor 15; IL-6: interleukin-6, KIM-1: kidney injury molecule 1, LTBR: lymphotoxin beta receptor, proADM: pro-adr-enomedullin, NGAL: neutrophil Gelatinase-associated Lipocalin, NT-proBNP: N-terminal pro-brain natriuretic peptide, NT-proCNP:N-terminal pro-C-type natriuretic peptide, PCT: procalcitonin, PIGR: Polymeric immunoglobulin receptor, PSAP-B: Prosaposin B, RAGE: Receptor for advanced glycation end product, sST-2: Soluble ST-2, TNF-R1: tumor necrosis factor alpha receptor 1, cTnI: cardiac troponin I, VEGFR-1: vascular endothelial growth receptor 1A, WAP-4C: WAP Four-Disulphide Core Domain Protein HE

Figure 1: Changes of medication during hospitalization