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Peripheral monocytosis as a predictive factor for adverse outcome in the emergency department

Survey based on a register study

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Abstract

Monocytosis is associated with chronic infections such as tuberculosis or endocarditis as well as rheumatic and myeloproliferative disorders. Monocytes are also involved in the pathogenesis of atherosclerosis, coronary artery disease, and stroke. The value of monocytosis as a prognostic marker in different diagnostic groups in the emergency setting, however, has not been investigated so far.

The aim of the article is to study monocytosis as an outcome factor in the emergency setting.

In a Swiss register study, we analyzed monocyte counts in 4238 patients aged >18 years who were admitted to the emergency department of a regional tertiary care hospital. Monocytosis was defined as 0.8×10^9 cells/L. Diagnoses were grouped into infection, cardiovascular, neurological, metabolic, gastrointestinal, pulmonary, or other. Thirty-day mortality was defined as the primary endpoint

A total of 1217 patients with monocytosis were identified. Patients with monocytosis at admission suffered more frequently from respiratory symptoms (17.7% vs 8.9%, $P<.001$) and infection as the final diagnosis (20.8% vs 10.3%, $P<.001$) while neurological diagnoses were significantly lower in the monocytosis group (15.3% vs 30.9%, $P<.001$). Patients with monocytosis suffered from more comorbidities such as congestive heart failure, chronic obstructive pulmonary disease, tumor, diabetes, or renal failure but not dementia. When adjusted for age, gender, comorbidities, and main diagnosis, the 30-day mortality ($P=.002$) and length of stay ($P=.001$) were significantly higher in patients with monocytosis. The 30-day mortality in patients with monocytosis was most notably influenced by a cardiological diagnosis (odds ratio 3.91).

An increased monocyte count predicts adverse outcome in patients admitted to the emergency department. Mechanistic studies will be necessary to specify the potentially detrimental role of monocytosis in critical illness.

Abbreviations: AMI = acute myocardial infarction, CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, ED = emergency department, HR = hazard ratio, ICU = intensive care unit, IQR = interquartile range, NRS = nutritional risk score, OR = odds ratio, WBC = white blood cell.

Keywords: cardiovascular, emergency department, infection, monocytosis, mortality, outcome, primary care

1. Introduction

Monocytes represent about 5% of all leukocytes in the peripheral blood.[1] After circulating for several days in the bloodstream, monocytes usually undergo extravasation. In the tissue they differentiate into macrophages or dendritic cells[2] and are involved in cytokine expression, antigen presentation, or phagocytosis.[3] "Patrolling" monocytes constantly migrate along the endothelium in blood vessels serving as vascular innate immune system.[4] Monocytes can be specified into different subsets such as $CD16^{high}14^{-}$ monocytes which produce high amounts of inflammatory cytokines such as tumor necrosis factor or a more regulatory $CD16^{low}14^{+}$ monocyte subset.[5,6]

As widely known monocytosis occurs in chronic infection such as tuberculosis, endocarditis, granulomatous disease, or in myeloproliferative disorders. Other disorders that can be associated with increased monocyte counts are the metabolic syndrome[7] and autoimmune disorders including rheumatoid arthritis.[8] The underlying pathophysiology leading to monocytosis is not fully understood. Chemokines such as monocyte chemoattractant protein-1 and growth factors trigger monocyte recruitment and homeostasis.[9] Smoking also leads to increased monocyte numbers.[10]

Monocytosis is associated with artherosclerosis and its consequences such as coronary artery disease, cerebrovascular disease, or kidney artery stenosis, for example, as a source of foam cells.[11,12] Increased monocyte counts after acute myocardial infarction (AMI) were associated with left ventricular dysfunction, left ventricular aneurysm, and other cardiac events.[13] Another study showed similar effects to the nonrecovery of the left

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ventricular function after reperfused AMI.[14] To this end, monocytosis has been identified as an independent risk factor for myocardial infarction or cerebral arterial disease.[15] The level of the National Institutes of Health Stroke Scale on stroke patients correlates with the amount of monocytes.[16]

So far, the prognostic value of monocytosis in the emergency setting has not been investigated although monocyte numbers usually are assessed in routine blood tests. In this Swiss register study we have analyzed monocytes counts in patients admitted to the emergency department as a predictive factor for survival and hospital stay.

2. Methods

2.1. Study design and setting

This is an observational, prospective cohort study. Between March 2013 and February 2014, consecutive adult medical patients were included upon hospital admission in the emergency department into the quality-control TRIAGE project. This project's main aim is to optimize the triage and patient flow of adult patients with medical emergency.[17]

As an observational quality control study, the Institutional Review Board (IRB) of the Canton of Aargau has approved the study and waived the need for informed consent (EK 2012/059).

2.2. Patient population and management

Adult in-patients with an acute medical illness were included in this study; children and surgical patients were excluded. We collected pertinent clinical information, including sociodemographic characteristics, main medical diagnosis, and comorbidities at hospital admission using the information routinely gathered from the hospital electronic medical system for coding of diagnosis-related group codes. This already available information supported the reliable assessment of baseline characteristics and different patient outcomes. Clinical information and patient outcomes were assessed until hospital discharge and structured patient interviews were conducted via telephone 30 days after hospital admission to assess information about different clinical and functional outcome measures such as location after discharge, quality of life, performance of activities of daily living, hospital readmission, and mortality. If a patient could not be reached, we contacted the family or the general practitioner to assess vital status.

2.3. Main diagnosis and comorbidities

Patients were divided into main diagnosis groups including infections, cardiovascular diseases, metabolic diseases, cancer, neurological disorders, digestive tract diseases, pulmonary diseases, and other disease. We also defined the following comorbidity groups: congestive heart failure, chronic obstructive pulmonary disease (COPD), dementia, diabetes mellitus, tumor, renal failure, and obesity.

2.4. Outcomes

Our primary outcomes were 30-day mortality, in-hospital mortality, length of stay, intensive care unit (ICU) admission, and rate of 30-day readmission assessed during the hospital stay and by telephone interviews at day 30.

Secondary outcomes included functional impairment and quality of life. Performance of daily living was measured by the Barthel index. We defined functional impairment as a Barthel index <95 points. In order to assess quality of life, we used the standardized measure of health EQ-5D including a descriptive system with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). These results were displayed as 2 levels, "impairments" or "no impairments."

2.5. Assessment of monocyte count and definition of monocytosis

Monocytes were counted using the automated hematology analyzer Sysmex XN or by hand in case of discrepancy. The Sysmes XN uses fluorescence and the SAFLAS method (Sysmes adaptive Flagging Algorithm based on Shape-recognition) for monocyte recognition.

The cut off for monocytosis was defined as 0.8×10^9/L blood, which is according to common literature. Monocytopenia was defined as 0.3×10^9 cells/L blood. Both thresholds were tested in this cohort regarding the 30-day mortality.

2.6. Statistical analysis

Categorical variables are expressed as percentages and counts or vice versa and continuous variables as medians (interquartile ranges: 25th–75th percentiles), unless stated otherwise. Frequency comparison was done by the χ^2 test. For all binary endpoints, logistic models with odds ratios (OR) and 95% confidence intervals (95% CI) were used. For time to hospital discharge, Cox regression models with hazard ratios (HR) were calculated. To adjust for possible confounds, we used 3 statistical models: model 1 for age and gender; model 2 for age, gender, and comorbidities; and model 3 for age, gender, comorbidities, and main diagnosis.

We evaluated the association between monocyte count and outcomes in the overall population as well as within different predefined subgroups based on gender, age (cut off 75 years) and main medical diagnosis. Evidence of effect modification within these subgroups was assessed by including interaction terms into the statistical models. A P value $<.05$ (for a 2-sided test) was considered statistically significant. All statistical analyses were performed with STATA 12.1 (Stata Corp, College Station, TX).

3. Results

3.1. Patient characteristics and comorbidities

The mean age in patients with monocytosis was higher compared to patients with normal monocyte counts (66 vs 61 years, $P<.001$, Table 1) and there were more male patients in the monocytosis group (65.7% vs 51.4%, $P<.001$). The nutritional risk status was higher in patients with monocytosis ($P=.001$) and accordingly, patients with monocytosis had lower albumin values ($P=.001$). Serum creatinine ($P=.001$), CRP ($P=.001$), and blood leukocyte count were also higher in the monocytosis group ($P=.001$). Diabetes ($P=.002$), tumor ($P<.001$), heart failure ($P=.022$), COPD ($P<.001$), renal failure ($P<.001$), and obesity ($P<.001$) were more prevalent in patients with monocytosis. Conversely, dementia was not more frequently observed in monocytosis ($P=.086$).

3.2. Symptoms and diagnosis

At admission, neurological symptoms (16.4% vs 29.7%, $P<.001$) and thoracic pain (14.9% vs 16.9%, $P<.001$) were lower in the monocytosis group whereas respiratory symptoms

Table 1

Patient characteristics overall and according to monocyte count (counts per liter blood stated).

n	Overall 4238	0.3–0.8×10⁹/L 2708	>0.8×10⁹/L 1217	*P* value
Age, median (IQR)	63 (46, 75)	61 (44, 75)	66 (50, 77)	<.001
Female gender, n (%)	1888 (44.6%)	1315 (48.6%)	418 (34.3%)	<.001
Male gender, n (%)	2350 (55.4%)	1393 (51.4%)	799 (65.7%)	<.001
NRS <3, n (%)	1165 (27.5%)	678 (25.0%)	400 (32.9%)	<.001
NRS ≥3, n (%)	375 (8.9%)	186 (6.9%)	128 (10.5%)	
NRS not assessed, n (%)	2698 (63.7%)	1844 (68.1%)	689 (56.6%)	
Initial blood biomarkers, median (IQR)				
Albumin, g/L	37.7 (34, 40.7)	38.4 (35.3, 41.0)	36.4 (32.1, 39.7)	<.001
Creatinine, μmol/L	85 (70, 105)	82 (68, 100)	91 (76, 116)	<.001
Calcium, mmol/L	2.26 (2.19, 2.35)	2.25 (2.18, 2.33)	2.29 (2.21, 2.39)	<.001
CRP, mg/L	17.9 (6.9, 68.9)	12 (6, 36)	34 (10, 110)	<.001
WBC, g/L	8.5 (6.7, 11.0)	7.8 (6.4, 9.4)	11.5 (9.3, 14.2)	<.001
Location after hospital/ED discharge, n (%)				
Home	1635 (38.6%)	998 (36.9%)	513 (42.2%)	.006
Other hospital	224 (5.3%)	151 (5.6%)	59 (4.8%)	.51
Nursing home	172 (4.1%)	107 (4.0%)	48 (3.9%)	.44
Rehabilitation clinic	197 (4.7%)	120 (4.4%)	58 (4.8%)	.42
Other or unknown	1897 (44.8%)	1283 (47.4%)	499 (41.0%)	<.001
In-hospital death	113 (2.7%)	49 (1.8%)	40 (3.3%)	<.001
Comorbidities, n (%)				
Diabetes	609 (14.4%)	357 (13.2%)	211 (17.3%)	.002
Tumor	630 (14.9%)	315 (11.6%)	200 (16.4%)	<.001
Congestive heart failure	250 (5.9%)	140 (5.2%)	90 (7.4%)	.022
COPD	204 (4.8)	107 (4.0%)	83 (6.8%)	<.001
Dementia	130 (3.1%)	84 (3.1%)	38 (3.1%)	.86
Renal failure	630 (14.9%)	344 (12.7%)	229 (18.8%)	<.001
Obesity	518 (12.2)	313 (11.6%)	181 (14.9%)	<.001
Main diagnosis, n (%)				
Infection	604 (14.3%)	278 (10.3%)	253 (20.8%)	<.001
Cardiovascular	944 (22.3%)	637 (23.5%)	272 (22.4%)	<.001
Metabolic	59 (1.4%)	35 (1.3%)	21 (1.7%)	.45
Cancer	213 (5.0%)	90 (3.3%)	68 (5.6%)	<.001
Neurological	1080 (25.5%)	838 (30.9%)	186 (15.3%)	<.001
Gastrointestinal	457 (10.8%)	250 (9.2%)	167 (13.7%)	<.001
Pulmonary	157 (3.7%)	78 (2.9%)	70 (5.8%)	<.001
Other	724 (17.1%)	502 (18.5%)	180 (14.8%)	.003
Main symptom at ED admission, n (%)				
Fever	237 (5.6%)	103 (3.8%)	89 (7.3%)	<.001
Diarrhea, vomitus, dysuria	265 (6.3%)	138 (5.1%)	92 (7.6%)	<.001
Nonthoracic pain	641 (15.1%)	413 (15.3%)	173 (14.2%)	.32
Thoracic pain	659 (15.6%)	457 (16.9%)	181 (14.9%)	<.001
Neurological symptoms	1060 (25.0%)	804 (29.7%)	199 (16.4%)	<.001
Respiratory symptoms	487 (11.5%)	240 (8.9%)	215 (17.7%)	<.001
Worsening of general condition	232 (5.5%)	116 (4.3%)	89 (7.3%)	<.001
Gastrointestinal bleeding	101 (2.4%)	64 (2.4%)	32 (2.6%)	.56
Other symptom	556 (13.1%)	373 (13.8%)	147 (12.1%)	.24

COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, ED = emergency department, IQR = interquartile range, NRS = nutritional risk score, WBC = white blood cell.

were more frequent (17.7% vs 8.9%, $P<.001$). Nonthoracic pain (14.2% vs 15.3%, $P=.32$) pain was similar. Worsening of the general condition (7.3% vs 4.3%, $P<.001$) and fever (7.3% vs 3.8%, $P<.001$) were also more likely in the monocytosis group.

In terms of diagnosis which let to hospital admission, neurologic disorders were identified in 15.3% versus 30.9% ($P<.001$) of the cases. Cardiovascular diagnosis as a reason for admission was similar in monocytosis in 22.4% versus 23.5% ($P<.001$) in patients with a normal monocyte count. The most notable increase was observed in the diagnosis of infection (20.8% vs 10.3%, $P<.001$). Gastrointestinal (13.7% vs 9.2%, $P<.001$), pulmonary (5.8% vs 2.9%, $P<.001$), or cancer (5.6% vs 3.3%, $P<.001$) diagnosis were higher in the monocytosis group.

3.3. Mortality, length of hospitalization and functional impairment

We studied mortality and length of hospitalization in different models (Table 2). Adjusted for age and gender, 30-day mortality ($P<.001$), length of stay ($P<.001$), and ICU admission ($P=.020$) were significantly higher in patients with monocytosis while in-hospital mortality ($P=.088$) and rate of 30-day admission ($P=.100$) were similar. When adjusted for age, gender, comorbidities, and main diagnosis, 30-day mortality ($P=.002$) and length of stay ($P=.001$) remained significant. In a subgroup analysis, the 30-day mortality was mostly influenced by cardiologic diagnosis (OR 3.91, Table 3) but without a significant effect modification. Conversely, there were no differences of

Table 2

Primary outcomes baseline overall and according to monocyte count.

n	Overall 4238	Monocytosis $> 0.8\times10^9$/L 1217	Unadjusted OR / HR (95%CI), *P* value	Model 1	Model 2	Model 3
30-day mortality, n (%)	218 (5.1%)	90 (7.4%)	2.24 (1.66–3.02), <.001	1.85 (1.36–2.52), <.001	1.71 (1.25–2.35), .001	1.69 (1.22–2.35), .002
In-hospital mortality, n (%)	113 (2.8%)	40 (3.3%)	1.84 (1.20–2.81), .005	1.46 (0.95–2.24), .088	1.31 (0.84–2.04), .232	1.25 (0.79–1.98), .330
Length of stay (median, IQR)	3 (1, 7)	4 (1, 7)	0.86 (0.79–0.94), .001	0.86 (0.79–0.94), .001	0.88 (0.80–0 .96), .004	0.85 (0.78–0.93), .001
ICU admission, n (%)	166 (3.9%)	60 (4.9%)	1.62 (1.15–2.27), .005	1.51 (1.07–2.11), .020	1.44 (1.02–2.03), .040	1.40 (0.99–1.99), .060
Readmission, n (%)						
No 30-day readmission	3406 (80.4%)	957 (78.6%)				
30-day readmission	414 (9.8%)	129 (10.6%)	1.21 (0 .96–1.52), .095)	1.21 (0.96–1.52),.100)	1.18 (0.94–1.49), .157	1.22 (0.96–1.54), .100
30-day readmission not assessed	418 (9.9%)	131 (10.8%)				

OR/HR for primary outcomes in patients with a monocyte count $>0.8\times10^9$/L compared to patients with a normal monocyte count. Adjusted for age /gender (Model 1), age/gender/comorbidities (Model 2), and age/gender/comorbidities/main diagnosis (Model 3).

CI = confidence interval, HR = hazard ratio, ICU = intensive care unit, IQR = interquartile range, OR = odds ratio.

Table 3

Subgroup analysis.

Outcome		Monocytosis $>0.8\times10^9$/L OR (95% CI), *P* value	*P* value for effect modification
30-day mortality	Overall	2.24 (1.66–3.02), <.001	
	Age		.991
	Age >75	2.11 (1.40–3.18), <.001	
	Age < 75	2.22 (1.34–3.29), .001	
	Gender		.836
	Female	2.05 (1.21–3.45),.007	
	Male	2.19 (1.51–3.17), <.001	
	Diagnosis		
	Infection	1.26 (0.62–2.58), .523	.095
	Cardiovascular	3.91 (1.87–8.18), <.001	.102
	Metabolic	0.53 (0.05–5.49), .597	.222
	Cancer	2.18 (1.07–4.47), .033	.893
	Neurological	2.10 (1.07–4.11), .031	.83
	Gastrointestinal	0.49 (0.13–1.83), .290	.017
	Pulmonary	1.92 (0.44–8.36), .383	.834
	Other	5.79 (1.72–19.47), .005	.103
ICU admission	Overall	1.62 (1.15–2.27), .005	
	Age, years		.021
	Age >75	0.76 (0.36–1.61), .475	
	Age <75	2.05 (1.40–3.02), <.001	
	Gender		.765
	Female	1.65 (0.89–3.05), .110	
	Male	1.47 (0.98–2.22), .064	
	Diagnosis		
	Infection	2.25 (0.76–6.67), .144	.582
	Cardiovascular	2.22 (1.28–3.84), .005	.177
	Metabolic	1.70 (0.10–28.70), .713	.973
	Cancer	Omitted	
	Neurological	0.49 (0.15–1.64), .249	.039
	Gastrointestinal	3.60 (0.92–14.13), .066	.245
	Pulmonary	0.97 (0.33–2.83), .959	.37
	Other	1.27 (0.44–3.72), .656	.665
30-day readmission	Overall	1.21 (0.96–1.52), .095	
	Age, years		.654
	Age >75	1.34 (0.83–2.15), .220	
	Age <75	1.19 (0.92–1.54), .193	
	Gender		.623
	Female	1.29 (0.89–1.86), .173	
	Male	1.15 (0.86–1.53), .345	
	Diagnosis		
	Infection	1.28 (0.70–2.35),.424	.88
	Cardiovascular	1.70 (1.09–2.65),.019	.088
	Metabolic	1.61 (0.32–8.17), .567	.731

(*continued*)

Table 3

(continued).

Outcome		Monocytosis $>0.8\times10^9$/L OR (95% CI), *P* value	*P* value for effect modification
	Cancer	0.95 (0.31–2.90), .926	.659
	Neurological	0.71 (0.38–1.34), .293	.068
	Gastrointestinal	2.03 (1.03–4.03), .042	.122
	Pulmonary	1.08 (0.39–2.99), .887	.825
	Other	0.95 (0.54–1.67), .853	.344
Functional impairment (Barthel <95)	Overall	1.24 (1.01–1.53), .04	
	Age, years		.117
	Age >75	0.98 (0.73–1.33), .912	
	Age <75	1.39 (1.02–1.88), .036	
	Gender		.249
	Female	1.46 (1.07–2.01), .018	
	Male	1.14 (0.87–1.51), .340	
	Diagnosis		
	Infection	0.77 (0.48–1.24), .282	.048
	Cardiovascular	1.47 (0.92–2.37), .111	.426
	Metabolic	1.82 (0.11–31.03), .678	.791
	Cancer	1.24 (0.51–3.02), .640	.986
	Neurological	1.55 (1.02–2.36), .042	.451
	Gastrointestinal	0.72 (0.35–1.48), .367	.105
	Pulmonary	0.95 (0.38–2.38), .921	.574
	Other	2.18 (1.24–3.83), .007	.033
Length of stay	Overall	0.86 (0.79–0.94), .001	
	Age, years		.079
	Age >75	0.96 (0.82–1.12), .605	
	Age <75	0.82 (0.74–0.92), <.001	
	Gender		.749
	Female	0.87 (0.75–1.01), .063	
	Male	0.85 (0.76–0.95), .006	
	Diagnosis		
	Infection	0.94 (0.76–1.17), .587	.398
	Cardiovascular	0.90 (0.75–1.09), .289	.591
	Metabolic	0.64 (0.32–1.28), .211	.542
	Cancer	0.86 (0.58–1.26), .426	.992
	Neurological	0.76 (0.61–0.94), .012	.444
	Gastrointestinal	0.78 (0.61–1.01), .055	.32
	Pulmonary	0.90 (0.61–1.33), .603	.901
	Other	0.86 (0.67–1.11), .254	.834

CI = confidence interval, HR = hazard ratio, ICU = intensive care unit, OR = odds ratio.

clinical functional impairment in the monocytosis versus normal monocyte count group (Table 4).

3.4. Functional impairment of patients

No differences were found in patients with monocytosis regarding functional impairment in terms of mobility ($P = .575$), usual activities ($P = .256$), self care ($P = .879$), pain or discomfort ($P = .366$), or anxiety ($P = .079$) (Table 4).

4. Discussion

Despite the profound knowledge in monocyte biology, surprisingly little is known about monocytosis in the clinical setting. In this large survey, we identified peripheral blood monocytosis as a negative prognostic marker in the emergency setting. This is in line with a plethora of previous studies showing that activation of the innate immune system may be detrimentally associated with critical illness.[18] Monocytes are a major source of oxidative stress and thus can trigger organ damage under certain circumstances.[19] Unfortunately, we could not specify the monocyte subsets in this study. The role of the 'inflammatory' $CD14^{++}CD16^{-}$ monocyte subset would be interesting and important in order to understand the mechanism of monocytes in critical illness.[20] Patients with monocytosis had more often respiratory symptoms and suffered from infection than individuals with normal monocyte counts. In part this might be related to the higher number of COPD patients in this group and indicates that smoking, which was not assessed in this study, triggers monocytosis. It can however be postulated that lung impairment, most likely due to infection, is a main stimulator of monocytosis. Fever, which was also associated with monocytosis in this study, further indicates that a potentially unspecific systemic inflammatory response is involved in monocytosis. Why neurologic diagnosis inversely correlated with monocytosis is unclear and surprising. Prior studies have shown an association between monocytes and cerebral vascular disease.[16] Potentially, patrolling monocytes at the inner side of the vessel wall behave differently in blood–brain barrier than in the rest of the circulation.

In contrast, cardiovascular diagnoses were the strongest influence for the 30-day mortality in patients with monocytosis. This is in line with previous studies showing that monocytosis is also involved in the pathogenesis of atherosclerosis. Apart from

Table 4

Secondary outcomes baseline overall and according to monocyte count. OR/HR for primary outcomes in patients with a monocyte count $>0.8\times10^9$/L compared to patients with a normal monocyte count. Adjusted for age /gender (Model 1), age/gender/comorbidities (Model 2), and age/gender/comorbidities/main diagnosis (Model 3).

n	Overall 4238	Monocytosis $>0.8\times10^9$/L 1217	Unadjusted OR / HR (95%CI), *P* value	Model 1	Model 2	Model 3
Functional impairment, n (%)						
No functional impairment (Barthel >95%)	3,448 (81.4%)	950 (78.1%)				
Functional impairment (Barthel <95%)	507 (12.0%)	158 (13.0%)	1.24 (1.01–1.53), .04	1.11 (0.89–1.38), .340	1.08 (0.87–1.36), .481	1.13 (0.89–1.42), .316
Barthel not assessed	283 (6.7%)	109 (9.0%)				
Mobility, n (%)						
No mobility limitation	1329 (31.4%)	405 (33.3%)				
Mobility limitation	341 (8.1%)	98 (8.1%)	0.93 (0.71–1.21), .575	0.94 (0.72–1.23), .660	0.91 (0.69–1.19), .481	0.89 (0.67–1.19), .436
Mobility not assessed	2568 (60.6%)	714 (58.7%)				
Usual activities, n (%)						
No usual activities limitation	1211 (28.6%)	378 (31.1%)				
Usual activities limitation	459 (10.8)	125 (24.9%)	0.87 (0.68–1.11), .256	0.91 (0.71–1.16), .439	0.88 (0.68–1.13), .314	0.89 (0.69–1.17), .409
Usual activities not assessed	2568 (60.6%)	125 (10.3%)				
Self-care, n (%)						
No self-care problems	1433 (33.8%)	431 (35.4%)				
Self-care problems	237 (5.6%)	72 (5.9%)	1.02 (0.76–1.39), .879	1.04 (0.76–1.42), .828	1.01 (0.73–1.39), .972	0.99 (0.71–1.39), .952
Self-care not assessed	2568 (60.6%)	714 (58.7%)				
Pain/discomfort, n (%)						
No pain/discomfort	1121 (26.5%)	348 (28.6%)				
Pain/discomfort	549 (13.0%)	155 (12.7%)	0.89 (0.72–1.13), .366	0.93 (0.74–1.18), .563	0.91 (0.72–1.15), .439	0.85 (0.67–1.08), .176
Pain/discomfort not assessed	2568 (60.6%)	714 (58.7%)				
Anxiety/depression, n (%)						
No anxiety/depression	1255 (29.6%)	394 (32.4%)				
Anxiety/depression	415 (9.8%)	109 (9.0%)	0.79 (0.62–1.03), .079	0.84 (0.65–1.08), .180	0.83 (0.64–1.07), .153	0.87 (0.67–1.13), .300
Anxiety/depression not assessed	2568 (60.6%)	714 (58.7%)				
EQ5D, n (%)						
No EQ5D problems	834 (19.7%)	271 (22.3%)				
EQ5D problems	1005 (23.7%)	287 (23.6%)	0.86 (0.71–1.06), .160	0.89 (0.72–1.09), .262	0.87 (0.70–1.07), .192	0.86 (0.69–1.07), .176
EQ5D not assessed	2399 (56.6%)	659 (54.1%)				
VAS EQ5D, median (IQR)	80 (60, 90)	80 (60, 90)				

CI = confidence interval, HR = hazard ratio, IQR = interquartile range, OR = odds ratio, VAS = visual analog scale.

the brain, we postulate that monocytosis is notably toxic to organs affected from atherosclerosis, for example, by increased extravasation or release of cytokines and oxidative stress. Monocytopenia was also associated with an increased 30-mortality (data not shown) in this survey but this mainly affected hematological disorders and was not influenced by cardiovascular diagnoses. Clearly, this study is observational and has several limitations. In this survey we cannot draw conclusions about mechanistic processes and we cannot answer the question whether monocytosis is the cause or just a consequence of adverse outcome. There was no negative effect of monocytosis on functional outcomes such as mobility or pain. We therefore conclude that in case of monocytosis, the activated innate immune system affects organ function, notably in patients with an already impaired cardiovascular system. Mechanistic studies are necessary in order to understand the negative role of monocytosis in critical care and to identify potential new treatment targets such as a monocyte-based immune modulation in critical care.

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