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Influence of functional deficiency of complement mannose-binding lectin on outcome of patients with acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Aims Experimental data point towards a favourable effect of low serum concentrations of complement mannose-binding lectin (MBL) on myocardial ischaemia/reperfusion (I/R) injury. As comparable data on the role of MBL in human I/R injury is lacking, we investigated the influence of low serum MBL concentrations on mortality of patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods and results Mannose-binding lectin was determined in 890 acute STEMI patients that were prospectively recruited in the APEX-AMI trial. This trial had a primary endpoint of death through Day 30 and secondary endpoints of death through Day 90 and the composite of death, cardiogenic shock, or congestive heart failure (CHF) through Days 30 and 90. Samples were taken immediately before PCI and the analysis of MBL limited to patients having received placebo. Patients with serum MBL levels of or below 100 ng/mL were considered to be functionally deficient. Of the 890 patients, 127 had functional MBL deficiency (14.3%). Characteristics of patients with MBL deficiency and those with MBL levels >100 ng/mL did not differ. In patients with MBL deficiency, there was 1 death (0.79%) compared with 42 deaths (5.51%) in patients with MBL levels >100 ng/mL ($P = 0.0233$) representing an absolute and relative lower mortality in MBL deficient patients of 4.7 and 85%, respectively. Functional MBL deficiency, however, was not associated with decreased risk of the combined endpoints of death and shock or death, shock, and CHF, respectively.

Conclusion Functional deficiency of complement MBL is associated with reduced mortality in patients with STEMI undergoing PCI. This unique finding suggests that a component of the innate immune system affects mortality in STEMI patients undergoing primary PCI.
Trial Registration: clinicaltrials.gov, Identifier: NCT00091637.

Keywords Myocardial infarction • PCI • Ischaemia/reperfusion • Complement • MBL

Introduction

Myocardial infarction is a leading cause of morbidity and mortality worldwide. As infarct size is a major determinant of mortality in myocardial infarction, limitation of infarct size has been an important objective of strategies to improve outcomes.[1] Currently, the most effective way to limit infarct size is to reperfuse ischaemic myocardium as soon as possible, e.g. by the use of percutaneous

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transluminal coronary intervention (PCI). Although early reperfusion is undoubtedly beneficial, the process of reperfusion itself results in inflammation and tissue damage named myocardial ischaemia/reperfusion (I/R) injury.[2–5] Therefore, a number of anti-inflammatory treatment strategies accompanying myocardial reperfusion have been investigated to reduce myocardial I/R injury.[6–8] However, these strategies have had limited success possibly, because the mechanisms involved in myocardial I/R are still not fully understood.

Mannose-binding lectin (MBL) is a pattern recognition molecule that is part of the complement cascade and the innate immune system. The name of the molecule is derived from its capacity to bind to terminal mannose groups that are found on a variety of pathogens as well as on apoptotic cells. Binding of MBL leads to the activation of complement via the so-called MBL pathway. Interestingly, due to genetic polymorphisms in the promoter region and three variant structural alleles of MBL up to 25% of the normal population have reduced serum concentrations of MBL and can be classified as being functionally deficient.[9]

The consequences of low levels of serum MBL in adults, i.e. functional MBL deficiency, are only partially understood. Whereas low levels of MBL correlated with recurrent infections in children,[10–12] the role of the MBL pathway in adults is less clear. The majority of individuals in the general population with low MBL levels do not suffer from recurrent infections nor seem high levels of MBL to be a problem.[13–16] However, in the cardiovascular system, there seems to be a fine balance as to when low MBL levels may be harmful[17–19] or beneficial[20,21] suggesting a role of MBL that is strongly dependent on the type of inflammation. In myocardial I/R injury[22,23] as well as in other settings of I/R injury,[24–27] experimental data point towards a favourable effect of low serum MBL. As comparable data on the role of MBL in human I/R injury is lacking, the aim of the present study was to investigate the correlation of low serum MBL concentrations with mortality of patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary PCI.

Methods

Study objectives

The study objective was to investigate the correlation of serum MBL concentrations with 90-day mortality alone or the combined endpoints of mortality and shock or mortality, shock, and CHF in patients with acute STEMI undergoing primary PCI.

In a sub-analysis, we investigated whether functional MBL deficiency was associated with reduced serum creatine kinase (CK) or CK-MB levels as well as with reduced markers of complement activation after 24 h after PCI.

Patients

All patients were prospectively recruited in the context of the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial.[28] In this trial, 5745 patients with STEMI from 17 countries and 296 sites were enrolled between 13 July 2004 and 11 May 2006.[7] Eligibility for enrolment required patients to be at least 18 years of age and to present within 6 h of symptoms that were deemed ischaemic and that had persisted for at least 20 min. Patients were expected to undergo primary PCI and were required to have high-risk electrocardiographic characteristics: these included at least 2-mm ST-elevation in two anterior lateral leads or at least 2-mm ST-elevation in two inferior leads coupled with ST-depression in two contiguous anterior leads for a total of 8 mm or more or a new left-bundle branch block with at least 1-mm concordant ST-elevation.

The outcome of patients having been treated with the complement C5 inhibitor pexelizumab did not differ from patients having received placebo.[7] However, as the treatment might have affected the analyses of complement MBL, in this study, we limited our analyses to patients receiving placebo. Thus, the present study included all patients from the APEX-AMI trial that had received placebo and in which serum taken at study inclusion was available (see below).

Patients were excluded if they had isolated inferior MI, were pregnant or breastfeeding, had known or suspected complement deficiency or active serious infection, or had other serious medical conditions likely to alter their recovery. Prior fibrinolytic therapy for treatment of the qualifying event was also a basis for exclusion. No upper age limit was set. The institutional review board of each participating hospital approved the protocol, and patients were required to provide written informed consent.

Definition of endpoints

The primary objective of the APEX-AMI trial was to determine whether pexelizumab reduced all-cause mortality through Day 30. Secondary objectives included the evaluation of pexelizumab's effect on death as well as the composite incidence of death, cardiogenic shock, or congestive heart failure (CHF) through Days 30 and 90. Tertiary objectives included stroke and recurrent MI at Day 90; sepsis through hospital discharge or Day 14, whichever occurred earlier; shock at Day 30; and 90-day composites of cardiogenic shock or CHF, death or cardiogenic shock, and death or CHF. Causes of death were recorded according to a standardized dictionary (Medra).

Congestive heart failure and cardiogenic shock were centrally adjudicated by a clinical events committee blinded to treatment assignment.[21] Congestive heart failure included new or worsening CHF occurring during the index hospitalization or rehospitalization for CHF as previously defined.[7]

Cardiogenic shock was defined as hypotension of less than 90 mmHg systolic blood pressure lasting for at least 1 h, not responsive to fluid resuscitation and/or heart rate correction, believed to be secondary to cardiac dysfunction, and associated with at least one of the following signs of hypoperfusion: cool, clammy skin, oliguria, altered sensorium, cardiac index less than or equal to 2.2 L/min/m^2.

Blood sampling and storage of sera

Blood markers were obtained in the context of the sub-study 'Inflammatory and other biomarkers' in preselected centres located predominately in the USA and Canada. Consecutive patients were recruited in these centres looking to a total of 2000 patients studied at baseline with the first 1000 studied at baseline and 24 h. The recruitment was stopped as the main trail was prematurely discontinued. A total of 890 consecutive placebo patients had serum collected for MBL determination at study inclusion and of 187 at baseline and 24 h. The tubes were left standing for 30–45 min for complete clot formation, and then centrifuged at 1800 *g* for 15 min at room temperature. The serum was then carefully transferred into cryovials and frozen locally to be shipped on dry ice at the Duke Cardiovascular Research Institute (Durham, USA) were they were kept at −80°C until transferred on dry ice to the Montreal Heart Institute (Montreal, Quebec, Canada) for batch analysis.

Determination of mannose-binding lectin and other complement parameters

Measurements of MBL concentrations were all performed on the same day as being thawed using the MBL Oligomer Elisa Kit 029 (Antibodyshop, Grusbakken, Denmark) run on an automated Robotic Adaltis ELISA instrument. The standard concentrations in these kits range from 0 to 40 ng/mL providing a range of 0–4000 ng/mL at 1/100 dilution. The coefficients of variation (CV) for the intra- and inter-assay reproducibility are 4 and 10%, respectively. Expected values in healthy humans are between 0 and 7000 ng/mL.

There is no unique definition of functional MBL deficiency and clinically relevant levels of MBL may differ in different diseases. In general, MBL levels <100 ng/mL are considered to be functionally deficient, whereas there is uncertainty in the range of 100–500 ng/mL (reviewed by Arslan *et al.*[8]). Therefore, MBL levels of or below 100 ng/mL were chosen for the definition of functional MBL deficiency. In a sub-analysis, patients with levels between 100 and 500 ng/mL, i.e. intermediate levels, were analysed separately.

The levels of the anaphylatoxins C4a and C3a were measured by a cytometric bead array (CBA) using the Human Anaphylatoxin BD kits (Biosciences, San Diego, USA). In these kits, beads of distinct fluorescence intensities are coated with specific capture antibodies specific to complement fragments. The fluorescence was analysed on an EPICS XL cytometer (Beckman Coulter, FL, USA), and measured using BD CBA Software, applying a four-parameter curve fit. The sensitivity of the assays for C4a is 10.5 pg/mL, and for C3a, 4 pg/mL. Intra-assay variation coefficients are between 3 and 5% for these tests, and inter-assays between 11 and 16%.

Soluble sC5b-9 complex was measured by the Enzyme Immunoassay Kit A009 (Quidel, San Diego, USA). This assay has a lower limit of the detection of 7.9 ng/mL at three standard deviations above the zero standard curves, and a lowest limit for quantification of 40 ng/mL. Intra- and inter-assay CV are 5 and 10%, respectively, with the range of values expected in healthy donors being between 40 and 6000 ng/mL and below <1000 ng/mL.

Statistics

Baseline characteristics, CK, CK-MB, and complement activation parameters are described depending on MBL measurements ≤100 ng/mL and those >100 ng/mL. Discrete factors are displayed as frequencies and continuous measurements displayed as the 25th, 50th, and 75th percentiles. In most cases, the χ^2 statistical comparison of categorical variables are reported. On occasion, when there were few cases or events the Fisher exact method is reported. For continuous variables, Wilcoxon rank sum was used to test for measures of association. The Kaplan–Meier method was used to report outcomes of interest for patients randomized to placebo that have baseline MBL measurements. Events, of interest, were death, death or shock and death, shock or CHF by Day 90 post-randomization. The Log-rank test statistic is reported for these analyses when MBL was being analysed as a dichotomous variable. Regression analyses of outcome data based on the Cox proportional hazards models were generated to assess MBL's ability to predict the events stated earlier. Hazard ratios with 95% confidence intervals and the Score test statistic and associated *P*-value are reported. Mannose-binding lectin levels were dichotomized into two and three groups, respectively, i.e. measurements ≤100 and >100 ng/mL or measurements ≤100 ng/mL, those between 100–500 ng/mL and ones >500 ng/mL.

All analyses were performed using SAS software (versions 8.2, SAS Institute, Cary, NC, USA).

Results

Serum mannose-binding lectin and patient characteristics mannose-binding lectin ≤100 vs. >100 ng/mL

Serum baseline MBL could be determined in all 890 patients. Of these patients, 127 had MBL levels of or below 100 ng/mL (14.3%) including 38 patients with undetectable MBL levels (4.3% of the study population). In order to investigate a potential acute phase reaction, MBL levels could also be determined at 24 h in 187 of the 890 patients. In these 187 patients, MBL levels at 24 h did not significantly differ from baseline MBL levels (median MBL at baseline 1446.1 ng/mL vs. MBL at 24 h 1536.1 ng/mL, $P = 0.98$). This lack of increase at 24 h was independent from baseline MBL levels.

Characteristics of patients with MBL ≤ 100 ng/mL compared with patients with MBL > 100 ng/mL did not differ and are summarized in *Table 1*.

Outcome of patients with mannose-binding lectin ≤100 vs. >100 ng/mL

The outcome of patients with MBL ≤ 100 ng/mL compared with patients with MBL > 100 ng/mL is shown in *Table 2*. In the group of patients with MBL levels ≤100 ng/mL, there was 1 death (0.79%) compared with 42 deaths (5.51%) in patients with MBL levels >100 ng/mL ($P = 0.023$). This corresponded to an absolute difference in mortality of 4.7% and a relative difference of 85% in favour of patients with low levels of MBL. The cumulative survival rate is shown in *Figure 1A*. In contrast, functional MBL deficiency was not associated with decreased risk of the combined endpoints of death and shock or death, shock and CHF, respectively, suggesting that low MBL levels affected mortality alone but not shock and heart failure (*Figure 1B*, $P = 0.676$).

As summarized in *Table 3*, most patients died of cardiovascular causes with cardiac arrhythmias and heart failure being the most frequent. In the cohort of patients with MBL levels >100 ng/mL, nine patients died of unknown and non-cardiovascular causes (1.2%) and 33 patients died due to cardiovascular events (4.3%). In comparison, the cause of death in the one patient who died in the cohort of patients with MBL levels <100 ng/mL was indicated as 'procedural and/or device related'.

Outcome of patients with mannose-binding lectin ≤100 vs. >100 ng/mL and ≤500 vs. >500 ng/mL

As it is unknown at which concentration MBL levels should be considered to be functionally deficient in the setting of myocardial I/R injury, patients with MBL levels above 100 ng/mL ($n = 763$) were separated into two sub-groups: patients with intermediate level of MBL, i.e. >100 and ≤ 500 ng/mL (140 of 763) and patients with high level of MBL, i.e. >500 ng/mL (623 of 763). As demonstrated in *Table 4*, patients with intermediate MBL serum levels had a similar outcome to that observed in patients with high levels of MBL, suggesting that the reduced mortality observed in patients

Table 1 Selected patient characteristics dependent on baseline serum mannose-binding lectin levels

Parameter	Baseline serum MBL		*P*-value
	MBL > 100 ng/mL	MBL ≤ 100 ng/mL	
n	763	127	
Age, median (year)	60 (51, 70)	60 (53, 73)	0.52
Female (%)	21.4	23.6	0.57
Prior CABG (%)	3.9	1.6	0.30
Prior PCI (%)	11.8	11.8	1.00
Prior MI (%)	13.2	15.7	0.44
Prior CHF (%)	2.9	3.9	0.57
History of diabetes (%)	16.9	12.6	0.22
Hyperlipidaemia (%)	49.7	53.3	0.49
Hypertension (%)	52.8	54.3	0.75
History of chronic inflammatory condition (%)	2.1	0.8	0.49
History of chronic liver disease (%)	0.8	1.6	0.32
Killip class >2 (%)	3.2	0.8	0.39
High risk inferior MI (%)	42.1	44.9	0.55
Heart rate, median (b.p.m.)	75 (64, 86)	76 (63, 86)	0.46
Systolic blood pressure, median (mmHg)	133 (116, 150)	132 (114, 148)	0.87
Body mass index, median	27.6 (24.8, 31.1)	27.1 (24.4, 31.0)	0.64
Time from symptom onset to angiography (ischaemic time), h, median	2.7 (1.9, 3.8)	2.4 (1.8, 3.7)	0.22

Values in parenthesis are 25th, 75th percentiles. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MI, myocardial infarction; CHF, chronic heart failure.

Table 2 Clinical outcome comparing patients with baseline mannose-binding lectin ≤100 vs. >100 ng/mL

Parameter, rate (95% confidence interval)	Baseline serum MBL (ng/mL)		Log-rank test statistic	*P*-value	Hazard ratio
	MBL > 100	MBL ≤ 100			
Death (Day 90)	5.51 (3.89–7.13)	0.79 (0–2.34)	5.1428	0.023	0.14 (0.02, 1.02)
Death or shock (Day 90)	8.01 (6.08–9.93)	3.97 (0.56–7.8)	2.4367	0.119	0.49 (0.20, 1.22)
Death, shock or CHF (Day 90)	13.24 (10.83–15.64)	11.83 (6.21–17.45)	0.1749	0.676	0.89 (0.52, 1.53)

with functional MBL deficiency was limited to patients with MBL levels ≤100 ng/mL.

Association of baseline mannose-binding lectin levels with creatine kinase, creatine kinase-MB, and complement activation products

As determined in a subgroup of patients, MBL deficiency was not associated with reduced peak CK or CK-MB levels. In addition, serum markers of complement activation could be measured in a small subgroup of patients before and 24 h after PCI. Mannose-binding lectin deficiency was not associated with significantly lower C4a, C3a, or sC5b-9 levels, neither in absolute levels nor in relative changes of levels between baseline and 24 h after PCI. However, in the relatively small subgroup of analysed patients with serum MBL ≤ 100 ng/mL, there was a trend towards lower levels of complement C4a 24 h after PCI indicating reduced complement activation via the classical and/or MBL pathway of complement. The data are summarized in *Table 5*.

Discussion

Primary PCI for acute STEMI provides a useful model for the study of myocardial I/R injury. In the present study, we observed that functional deficiency of the complement component MBL is associated with reduced 90-day mortality in patients with acute myocardial infarction undergoing early reperfusion by catheter revascularization. The relative difference in mortality was about 85% compared with patients with sufficient serum MBL levels. Thus, for the first time, a component of the complement cascade and the innate immune system could be shown to correlate with mortality in a human I/R situation.

Interestingly, functional MBL deficiency seemed to affect mortality alone but not the combined endpoint of death, shock, and

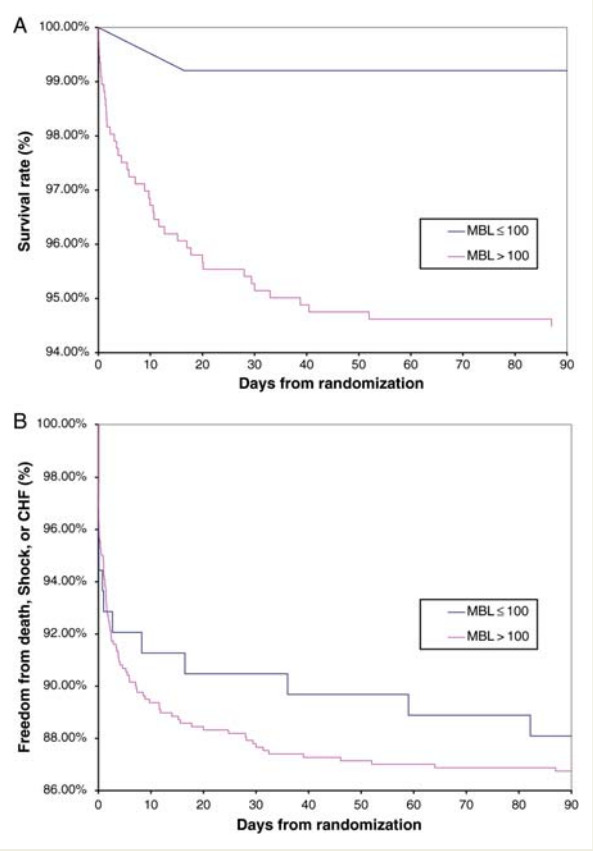

Figure 1 Relationship between serum mannose-binding lectin (MBL) levels and survival rate (*A*) or the combined endpoint of death, shock, and congestive heart failure (CHF) (*B*) in patients with acute ST-elevation myocardial infarction having undergone primary percutaneous coronary intervention. *P*-values were 0.023 and 0.676, respectively.

Table 3 Cause of death comparing patients with baseline mannose-binding lectin ≤100 vs. >100 ng/mL

Cause of death	Baseline serum MBL (ng/mL)	
	MBL > 100	MBL ≤ 100
Sudden cardiovascular death	14	1
Heart failure	6	0
Cardiac arrhythmia	5	0
Cardiac valve disorders	1	0
Coronary artery disorders	1	0
Fatal outcomes	1	0
Procedural and device related injuries and complications	0	1
Non-sudden cardiovascular death	19	0
Heart failure	8	
Cardiac arrhythmia	10	
Myocardial disorders, unspecified	1	
Not cardiovascular-related death	7	0
Respiratory disorders	2	
Central nervous system vascular disorder	1	
Respiratory and mediastinal neoplasms, malignant, and unspecified	1	
Reproductive neoplasms male, malignant, and unspecified	1	
Infections, pathogen class unspecified	1	
Gastrointestinal ulceration and perforation	1	
Unknown cause of death	2	0

CHF. We could also not observe differences in CK and CK-MB levels between MBL sufficient vs. functionally deficient patients, suggesting that MBL levels did not affect the size of infarction. However, when analysing the causes of death, most patients died for cardiovascular reasons with cardiac arrhythmias and heart failure being the most frequent events. Therefore, inflammatory I/R injury seemed to affect the severity but not the rate of events after reperfusion. We hypothesise that low MBL mostly reduced the rate of fatal arrhythmia in patients with severe heart failure, whereas the degree of heart failure due to ischaemic tissue remained unchanged.

Functional MBL deficiency is frequent and seems to be the most frequent immunodeficiency in man. In our study, a functional MBL deficiency defined as MBL levels ≤100 ng/mL could be found in 14% of the study population which is in or slightly above the range described by previous studies.[15,29–32] This observation is in line with clinical as well as experimental reports describing that low MBL is a risk factor for and is involved in the development of atherosclerosis.[17,20,33] It also indicates that our data are of importance for a significant part of the general population and supports the view that I/R injury leads to significant inflammatory tissue damage that limits the benefits achieved by the reperfusion procedure. As a consequence, anti-inflammatory treatment strategies in I/R injury should have the potential to improve the outcome of patients undergoing reperfusion procedures significantly. In this context, and similar to observations made in animal studies, MBL might serve as treatment target itself with the aim to inhibit the function of MBL in patients who are not already genetically deficient.[22]

Independent of potential therapeutic consequences, our data contribute to the understanding of the role of complement in human myocardial I/R injury. In I/R injury, complement activation was described during myocardial infarction almost 40 years ago[34] and has led to numerous investigations on the contribution of the complement system to I/R tissue injury. Combined data from a number of studies suggest that following I/R, complement may be activated through all three pathways of complement: the classical, the alternative pathway, and the lectin pathway. However, the exact mechanisms by which the complement system is activated after I/R are not well established (reviewed in 35,36). In line with our data, recent experimental studies suggested that myocardial I/R injury might lead to damaging complement activation that at

Table 4 Clinical outcome comparing patients with baseline mannose-binding lectin ≤100 vs. >100 ng/mL but ≤500 vs. >500 ng/mL

Parameter, rate (95% confidence interval)	Baseline serum MBL (ng/mL)			Log-rank test statistic	*P*-value
	MBL > 500	MBL > 100 and ≤500	MBL ≤ 100		
Death (Day 90)	5.46 (3.67–7.24)	5.76 (1.88–9.63)	0.79 (0–2.34)	5.16	0.076
Hazard ratio[a]		1.05 (0.49, 2.27)	0.14 (0.02, 1.04)		
Death or shock (Day 90)	7.54 (5.47–9.62)	10.07 (5.07–15.08)	3.97 (0.56–7.8)	3.5124	0.173
Hazard ratio[a]		1.35 (0.75, 2.46)	0.52 (0.21, 1.31)		
Death, shock or CHF (day 90)	13.00 (10.36–15.64)	14.30 (8.50–20.10)	11.83 (6.21–17.45)	0.3744	0.83
Hazard ratio[a]		1.12 (0.69, 1.82)	0.91 (0.52, 1.58)		

[a]Reference cell for reporting the hazard ratios is those with MBL values >500 ng/mL.

Table 5 Creatine kinase, creatine kinase-MB and complement activation parameters dependent on baseline serum mannose-binding lectin levels

Parameter, median (25th, 75th percentile)	Patients (*n*)	Baseline serum MBL		*P*-value
		MBL > 100 ng/mL	MBL ≤ 100 ng/mL	
Peak CK	625	1700 (772, 3134)	1452 (798, 3156)	0.614
Peak CK-MB	575	156.5 (66.1, 239.2)	148 (71.0, 286.0)	0.850
24 h C3a	105	266147 (198913, 381447)	332385 (240026, 403601)	0.431
Absolute change in C3a	105	8980 (−59364, 83849)	−7815 (−43816, 82705)	0.823
Relative (%) change in C3a	105	3.7 (−22.2, 48.5)	−1.1 (−11.7, 33.7)	1.000
24 h C4a	108	214627 (146980, 302809)	170970 (144000, 202238)	0.140
Absolute change in C4a	108	20708 (−12943, 73182)	−8755 (−30994, 26556)	0.088
Relative (%) change in C4a	108	11.8 (−8.3, 41.1)	−0.7 (−30.8, 18.3)	0.087
24 h sC5b-9	96	845 (525, 1448)	736 (382, 1447)	0.489
Absolute change in sC5b-9	89	346 (21, 959)	258 (8, 1044)	0.833
Relative (%) change in sC5b-9	89	95.8 (11.1, 333.5)	101.4 (−0.4, 261.0)	0.843

Concentrations of C3a, C4a are given in pg/mL and sC5b-9 in ng/mL. Creatine kinase and CK-MB are given in U/l.

least in part is mediated by the MBL pathway.[22,23] Our observations that MBL deficiency is associated with reduced mortality after PCI for acute myocardial infarction support the view that complement MBL plays an important role in myocardial I/R injury. Interestingly, this effect could only be seen in patients with very low MBL levels, i.e. ≤100 ng/mL, suggesting that there is no continuous relation between mortality and MBL levels. There rather seems to be a critical concentration of MBL that distinguishes between sufficient or insufficient complement activation in the context of I/R injury. In a small subgroup of patients, we could analyse whether functional MBL deficiency indeed was associated with reduced levels of complement activation products 24 h after PCI. Such an association could not be found. However, there was a trend towards lower levels of the complement split product C4a when compared with patients with high levels of complement MBL which is compatible with reduced complement activation via the MBL pathway. Considering the fact that the generation of C3a and sC5b-9 seems to be independent of the MBL level additional complement activation via the alternative pathway seems to be likely.

Independent of the pathway of complement relevant for the activation in I/R injury, it also remains to be determined whether MBL is involved in other types of human I/R injury such as intestinal or renal I/R injury as suggested by experimental studies.[24–26]

It is important to note that the study was powered to detect a relative difference of 50% of the combined endpoint of death, shock, or heart failure in MBL deficient patients but not for a 50% reduction of mortality alone. Thus, the large effect seen in MBL deficient individuals may represent an overestimate of the true effect and be a chance result. Therefore, our data needs to be confirmed in further studies. In addition, our study is of descriptive nature and therefore cannot identify a causal relationship between functional MBL deficiency and reduced mortality in patients with STEMI undergoing PCI. However, the results are well in line with observations made in experimental models[22,23]

and in this trial an affect on mortality alone in patients with low MBL levels was observed despite low overall mortality.

In conclusion, functional deficiency of complement MBL was associated with reduced mortality in patients with acute STEMI undergoing primary PCI. Thus, MBL seems to contribute to fatal secondary inflammatory damage of the reperfused ischaemic heart muscle and might serve as a target for treatment strategies aiming to reduce myocardial I/R injury.

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Conflict of interest: none declared.

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