In patients with STEMI, Lactate DeHydrogenase (LDH) elevation may occur early after symptom onset and is associated with poor outcome

Outcome of elevated LDH on admission in STEMI

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Abstract

Elevation of LDH on admission is often used as a sign of late presentation, however, only few studies evaluated the relationship between LDH elevation and time of presentation. In addition, the impact of elevated LDH before primary PCI on angiographic- and clinical outcome is unknown. A large scale, prospective, observational single-centre study was performed in all consecutive STEMI patients who underwent primary PCI. LDH was measured upon arrival in the PCI centre. Patients who had LDH measurement >1 hour after admission were excluded. The independent association between elevated LDH on admission and 30-day- and 1-year mortality was evaluated using Cox proportional Hazard models. Elevated LDH was present in 20.0% of patients. In patients with <150 minutes of symptoms, LDH was elevated in 14.6%. Patients with elevated LDH were older, more often female, had a higher TIMI risk score and Killip class on admission. Elevated LDH on admission was associated with poor angiographic and clinical outcome (TIMI 3 flow post-PCI 85.5%, no-reflow in 14.5%, 30-day mortality 13.5%). At multivariate analyses, elevated LDH on admission remained a strong predictor of 30-day (HR 8.5, CI 95%:5.6–13.0) and 1-year mortality (HR 3.4, CI 95%:2.3–5.0) independent of time from the onset of symptoms. Elevation of LDH may occur early after the onset of symptoms in STEMI patients who are planned to undergo primary PCI and is associated with poor angiographic and clinical outcome, irrespective of time from symptom onset. Elevated LDH on admission is a strong and independent predictor of short and long-term mortality.

Key words: lactate dehydrogenase, symptom onset, STEMI, percutaneous coronary intervention

1. Introduction

The improvement in the management of patients with ST-elevation myocardial infarction (STEMI) characterized by early diagnosis and treatment of the acute event, improved management of complications, and general availability of pharmacologic and mechanical therapies has significantly reduced cardiac mortality.[1-5] In daily practice, the treatment of STEMI is often based on the duration of symptoms before hospital arrival. The administration of thrombolytic therapy is often considered in patients presenting early after the onset of symptoms. However, the time from symptom onset is often difficult to assess and not always reliable. Elevation of lactate dehydrogenase (LDH) on admission is often used as a sign of late presentation, however, only few studies evaluated the relationship between LDH elevation and time of presentation. In addition, the impact of elevated LDH before primary percutaneous coronary intervention (PCI) on angiographic and clinical outcome is unknown. The aim of the study was to evaluate the relationship between elevated LDH on admission and time from onset of symptoms in patients with STEMI treated with primary PCI. In addition, the association between elevated LDH and angiographic and clinical outcome was assessed.

2. Methods

2.1 Population

From 16 October 2005 to 31 December 2009, individual patient data from all consecutive patients with admission diagnosis of STEMI admitted for primary PCI at our hospital were prospectively recorded. To avoid double inclusion of patients, only the first recorded admission for STEMI during the study period was used. Patients were diagnosed with STEMI if they had chest pain for >30 minutes and ECG changes with ST segment elevation >2 mm in at least 2 precordials and >1 mm in the limb leads. All patients presenting within 6 hours from symptom onset or between 6 and 24 hours if they had continuous

symptoms and signs of ischemia (persistent or recurrent chest pain and/or persistent elevation or re-elevation of ST-segment) were included. Patients who had LDH measurement >1 hour after admission were excluded. According to the protocol all patients received 500 mg of aspirin intravenously, 600 mg clopidogrel orally and 5000 IU intravenous unfractionated heparin (UFH). In some patients additional treatment with glycoprotein IIb/IIIa inhibitors (GPI) (25µg/kg bolus tirofiban) was given in the ambulance or referral centre. All patients were directly transported to the cath-lab on arrival and acute coronary angiography was performed with subsequent primary PCI when indicated as part of routine treatment for all STEMI patients in our hospital. Primary PCI was routinely performed by femoral access using 6 French sheaths with selective thrombus aspiration and stent implantation where appropriate. All patients were treated with optimized drug therapy including angiotensin-converting enzyme inhibitors, β-blockers and lipid-lowering drugs where appropriate. Patients were stratified into elevated LDH and normal LDH on admission. Baseline characteristics, angiographic outcome and clinical outcome were compared between the groups.

2.2 Measurements (end points, definitions)

The primary endpoint was the relationship between elevated LDH on admission and time from onset of symptoms. The key secondary endpoint was the association of elevated LDH on admission and angiographic (including no-reflow) and clinical outcome. No-reflow was defined as TIMI 2 or 3 flow during PCI and TIMI 0-2 flow after PCI. Enzymatic myocardial infarction size was estimated by peak CK in IU/L in the first 48 hours after the acute event, as previously described. [6]

2.3 Serum marker analysis

Blood samples were drawn on admission. Heparin plasma LDH

concentrations were analyzed with the Elecsys 2010 system (Roche Diagnostics, Almere, The Netherlands). LDH activity was determined enzymatically on a Roche/Modular automatic analyzer according to the International Federation of Clinical Chemistry (IFCC) recommendation at 37^{o}C.[7] LDH was elevated when its value was above 250 U/L, based on the reference interval in healthy individuals. Protocol-specified blood sampling for CK levels was performed at baseline and at 8 hours, 16 hours, 24 hours and 48 hours after PCI. Measurement of serum total CK levels was performed on the Modular system (Roche Diagnostics).

2.4 Angiographic and Electrocardiographic analysis

All angiograms have been reviewed by two experienced investigators who were blinded to all data apart from the coronary angiogram. TIMI flow grades and myocardial blush grade (MBG) were assessed after the PCI procedure, as previously described.[8,9] Residual stenosis was assessed visually. Procedural success was defined as postprocedural TIMI 3 flow in the infarct related vessel in combination with a myocardial blush grade 2 or 3 and a residual stenosis less than 50%. The sum of ST-segment deviation in all 12 leads was measured 20 ms after the end of the QRS complex with a caliper. We calculated both residual ST segment-deviations on the single ECG after PCI and ST-segment deviation resolution from paired ECGs. Patients were divided into four groups of residual ST-segment deviation (0 mm: normalized ST segment and no residual ST-segment deviation; 1–3 mm; 4– 6 mm; and >6 mm) and into three groups of ST-segment deviation resolution (complete: >70% resolution; partial: >30% but <70% resolution; and no resolution: <30% resolution), as described previously. [10]

2.5 Data collection and follow-up

Patient characteristics were prospectively acquired on admission using either case record forms or using a computer-based database and patients

were followed up for one year by use of hospital records, questionnaire and telephone contact. For patients who died during follow-up, hospital records and necropsy data were reviewed. Follow-up was performed by independent research nurses not involved in patient treatment. Study approval was obtained from the medical ethic committee from our institution and all patients gave informed consent.

2.6 Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.1. Continuous data were expressed as mean ± standard deviation and categorical data as percentage, unless otherwise denoted. Differences between continuous data were performed by student's t test and the chi-square or Fisher's exact test was used as appropriate for dichotomous data. Multivariate Cox proportional-hazards regression analyses were performed to determine the independent association of elevated LDH on admission and 30-day- and 1-year mortality, selecting baseline variables with entry/stay criteria of $p<0.10$. Variables entered into the model included age, gender, diabetes mellitus, renal insufficiency, anterior infarction, Killip class >1, symptom onset to arrival PCI centre >6 hrs, three vessel disease, and elevated LDH on admission. Kaplan-Meier curves were constructed for 1-year mortality. For all analyses, statistical significance was assumed when the two-tailed probability value was <0.05.

3. Results

3.1 Baseline characteristics

During the study period 3393 patients were included, of whom 940 patients had LDH measurement >1 h after admission. The remaining 2453 patients form the basis of this report (figure 1). Of the 491 patients (20.0%) with elevated LDH on admission, CK-MB and troponin T were also positive in 72.1% and 85.7% of the patients. Baseline characteristics of the study group stratified by admission LDH are listed in table 1. Patients with

elevated LDH were older, more often female, had a higher TIMI risk score and Killip class on admission. In the normal LDH group the diagnosis of STEMI was made more often in the ambulance compared to the elevated LDH group (75,1% vs 63,1%, p<0.001). Elevated LDH was associated with a longer time from symptom onset to arrival PCI centre, and a longer ischemic time. However, in patients with less than 2 hours and 30 minutes from symptom onset to arrival PCI centre, LDH was elevated in 14.6% of patients. The prevalence of elevated LDH on admission according to symptom onset to arrival PCI centre is depicted in figure 2.

3.2. Angiographic- and electrocardiographic outcome

In table 2 angiographic and electrocardiographic outcome is shown. Post-PCI TIMI 3 flow and MBG 3 were both significantly lower in patients with elevated LDH (85.5% vs 94.3%, p<0.001 and 38.1% vs 53.9%, p<0.001). No-reflow occurred significantly more often in patients with elevated LDH on admission compared to patients with normal LDH (14.5% vs 5.7%, p<0.001). Furthermore, the admission ECG showed a higher degree of ST elevation and more often showed the presence of Q waves in patients with elevated LDH on admission. After PCI, the extent of residual ST segment deviation was also higher in this group.

3.3 Clinical outcome

Clinical outcome is summarized in table 3a. Elevated LDH was associated with a larger infarct size (median (IQR): 1899 (76 –3640) vs 1150 (447–2460), p<0.001) and a higher 30-day MACE rate (18.6% vs 5.0%, p<0.001) as compared to patients with normal LDH on admission. Thirty day as well as 1-year mortality was significantly higher in patients with elevated LDH compared to patients with normal LDH on admission (30-day: 13.5% vs 1.7%, p<0.001, 1-year: 21.3% vs 4.4%, p<0.001).

3.4 Early Presenters

In those patients who presented within 2.5 hours (150 minutes, median time from onset of symptoms), admission LDH was elevated in 14.6% of patients. Also these early presenting patients had a significantly higher 30-day- and 1-year mortality as compared to the group of early presenters with normal LDH (16.1% vs 1.7%, and 23.0% vs 5.1%, both p<0.001, table 3b and figure 3).

3.5 Multivariate predictors of 30-day and 1-year mortality

In the multivariate analysis (table 4), adjustments were made for age, gender, diabetes mellitus, renal insufficiency, time from symptom onset to arrival PCI centre >6 hrs, Killip class >1, anterior infarction, three vessel disease, and elevated LDH on admission. Independent predictors of 30-day mortality were age (HR 1.04, 95% CI 1.02-1.07), Killip class >1 (HR 2.7, 95% CI 1.5-4.8), renal insufficiency (HR 2.2, 95% CI 1.3-3.9), three vessel disease (HR 1.8, 95% CI 1.1-3.1) and elevated LDH on admission (HR 8.5, 95% CI 5.6-13.0). Furthermore, elevated LDH was also an independent predictor for 1-year mortality (HR 3.4, CI 95%, 2.3-5.0) (table 5).

4. Discussion

The major finding of this analysis is that elevation of LDH may occur early after the onset of symptoms in patients with STEMI who are planned to undergo primary PCI. In addition, it was found that patients with elevated LDH on admission have worse angiographic (including no-reflow) and clinical outcome. Elevated LDH on admission was a strong and independent predictor of 30-day and 1-year mortality, despite timely primary PCI. Our data show that this occurs, irrespective whether they present early or late. To the best of our knowledge, these findings have not been published in previous reports.

4.1 Mechanism for worse outcome

Elevated LDH patients presented with a higher prevalence of several comorbid conditions including diabetes, hypertension and renal failure. They more

often presented with signs of heart failure (Killip class >1), a higher TIMI risk score and a longer ischemic time than patients with normal LDH on admission. These clinical variables have a strong influence on outcome. However, after correction for these differences in baseline characteristics by multivariate analysis, elevated LDH on admission remained the strongest independent predictor of 30-day- and 1-year mortality.

4.2 Time dependence and elevated LDH

Patients with elevated LDH on admission have a worse outcome, irrespective whether they present early or late, as is shown by the Kaplan-Meier survival curve (figure 3). The higher incidence of Q waves on presentation suggests that infarctions are older in the group with elevated LDH on admission, despite short standing symptoms: (14.6% of patients with elevated LDH presented within 2 hours and 30 minutes from symptom onset). However, Q waves were also present in 33% of patients who presented without elevation of LDH. This confirms the finding that also the presence of Q waves might occur early after the onset of symptoms as was found in a recent study [11] and confirms that a short duration of symptoms is not always associated with good outcome. Another finding is that patients with elevated LDH on admission have a greater area at risk: they have a higher cumulative ST elevation on the admission ECG, more often have an anterior MI and more often present with heart failure. The larger the area at risk, the earlier the washout of cardiac enzymes will start, as was previously demonstrated.[12] All these characteristics are predictive of a reduced effectivity of myocardial reperfusion. De Luca and co-workers previously found that these patients have reduced myocardial blush and/or ST resolution despite successful epicardial revascularization.[13] This suggest that LDH elevation on admission is a simple marker predictive of poor reperfusion and consequently clinical outcome. Another

explanation for the elevated cardiac enzymes despite relatively early presentation might be the fact that plaque instability occurred several days or weeks before occlusive coronary thrombosis. Repetitive embolization of activated thrombus might have induced small areas of necrosis before full coronary occlusion. Therefore one may speculate that patients who present with recent onset of symptoms but with already elevated LDH might have had episodes of plaque instability before coronary occlusion, as was shown previously by work from Rittersma and co-workers.[14] The same group also found that thrombus composition and thrombus age (>1 day) were associated with clinical outcome.[15]

4.3 Limitations

This study is a post hoc observational analysis of all consecutive STEMI patients enrolled at our institution, and therefore represents daily clinical practice. First, baseline characteristics between the two groups were not similar for all variables: this probably reflects a true difference between patients with and without elevated LDH on admission. Second, our study shows that time from symptom onset to arrival PCI centre is less important for the outcome of the patient than characteristics such as elevated LDH and hemodynamic variables. Furthermore, our data show that time from symptom onset is unreliable in STEMI patients. The onset of symptoms does not always represent the start of the infarction. So, symptom onset should be a less important criterion for decision-making-strategy in STEMI patients. However, some of the important consequences of time, such as early out-of-hospital death, are not represented in our data. Third, electrocardiographic outcomes were available in only 34% of the patients. Finally, LDH is slightly cardiospecific, however, in respectively 72.1% and 85.7% of the patients with elevated LDH on admission, CK-MB and troponin T were positive on admission.

4.4 Conclusion

Elevation of LDH may occur early after the onset of symptoms in patients with STEMI who are planned to undergo primary PCI. Irrespective of time from symptom onset to arrival PCI centre, STEMI patients with elevated LDH on admission have a poor angiographic and clinical outcome. Elevated LDH on admission was a strong and independent predictor of 30-day- and 1-year mortality. The exact mechanism why patients with LDH elevation on admission do much worse remains to be determined.

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Table 1: Baseline characteristics of patients with and without elevated LDH

Baseline	Normal LDH N= 1962	Elevated LDH N= 491	P value
Age	63.1 12.4	66.2 12.9	<0.001
Female gender	483/1962 (24.6%)	167/491 (34.0%)	<0.001
Hypertension	681/1956 (34.8%)	201/490 (41.0%)	0.011
Smoking	794/1938 (41.0%)	174/488 (35.7%)	0.032
Diabetes Mellitus	226/1958 (11.5%)	69/490 (14.1%)	0.123
Previous MI	207/1955 (10.6%)	43/491 (8.8%)	0.231
Previous PCI	200/1956 (10.2%)	36/491 (7.3%)	0.052
Renal insufficiency	307/1959 (15.7%)	135/491 (27.5%)	<0.001
Timi risk > 3	603/1928 (31.3%)	267/485 (55.1%)	<0.001
Killip > 1 on admission	89/1959 (4.5%)	93/491 (18.9%)	<0.001
Diagnosis in ambulance	1471/1959 (75.1%)	310/491 (63.1%)	<0.001
SO to diagnosis, min (IQR)	83 (45 – 154)	144 (62 – 497)	<0.001
SO to arrival PCI centre, min (IQR)	140 (99 – 220)	217 (120 – 590)	<0.001
SO to arrival PCI centre > 6 hrs	172/1527 (11.3%)	154/436 (35.3%)	<0.001
Ischemic time, min	192 (145 – 296)	299 (183 – 734)	<0.001
Ischemic time > 180, min	886/1591 (55.7%)	275/366 (75.1%)	<0.001
Door to balloon time (min)	44 (29 – 70)	52 (35 – 88)	<0.001
Q wave on diagnosis ECG	440/1338 (32.9%)	176/308 (57.1%)	<0.001
Cum ST deviation on diagnosis ECG	13.3 9.2	14.5 11.9	0.093
GP IIb/IIIa pre-PCI	947/1934 (49.0%)	200/488 (41.0%)	0.002
Bail-out GP IIb/IIa	406/1934 (21.0%)	98/488 (20.1%)	0.658

Data are n/N (%) or mean (SD), or median (IQR). BMI=body mass index. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. GFR= glomerular filtration rate. BP=blood pressure. SO=symptom onset. GP=glycoprotein.

Renal insufficiency= creatinine clearance <60 ml/min (as calculated by MDRD). Elevated LDH= LDH≥250 U/L

Table 2: Angiographic, electrocardiographic- and laboratory outcomes of patients with and without elevated LDH

Baseline	Normal LDH N=1962	Elevated LDH N=491	P value
Three vessel disease	351/1928(18.2%)	96/458 (21.0%)	0.174
RCA	773/1827(42.3%)	140/442 (31.7%)	<0.001
LAD	748/1827(40.9%)	226/442 (51.1%)	<0.001
RCX	268/1827(14.7%)	57/442 (12.9%)	0.340
Angiography performed	1937/1961 (98.8%)	461/491 (93.9%)	<0.001
Initial TIMI flow			0.013*
0,1	1056/1713 (23.1%)	265/389 (68.1%)	
2	261/1713(15.2%)	54/389 (13.9%)	
3	396/1713(23.1%)	70/389 (18.0%)	
PCI immediately after CAG	1641/1681 (97.6%)	372/391 (95.1%)	0.008
Thrombus aspiration	346/1921(18.0%)	89/466 (19.1%)	0.585
IABP	107/1921 (5.6%)	82/466 (17.6%)	<0.001
TIMI post-PCI			<0.001*
0	25/1677(1.5%)	8/387 (2.1%)	
1	6/1677 (0.4%)	9/387 (2.3%)	
2	65/1677(3.9%)	39/387 (10.1%)	
3	1581/1677 (94.3%)	331/387 (85.5%)	
TIMI 0-2 (no-reflow)	96/1677(5.7%)	56/387 (14.5%)	<0.001
MBG			<0.001*
0	32/1211(2.6%)	20/223 (9.0%)	
1	111/1211 (9.2%)	50/223 (22.4%)	
2	415/1211(34.3%)	68/223 (30.5%)	
3	653/1211(53.9%)	85/223 (38.1%)	
MBG 0-1	143/1211(11.8%)	70/223 (31.4%)	<0.001
Electrocardiographic			
ST resolution diagnosis 1 h after PCI			<0.002
Complete	306/544 (56.3%)	35/95 (36.8%)	

Partial	140/544 (25.7%)	33/95 (34.7%)	
No	98/544 (18.0%)	27/95 (28.4%)	
Residual ST deviation 1 h after angiography/PCI	4.8 6.3	6.7 5.7	<0.001
Residual ST deviation > 3mm 1 h after angiography/PCI	433/959 (45.2%)	137/205 (66.8%)	<0.001
Laboratory outcomes			
First CK positive**	480/1962 (24.5%)	377/491 (76.8%)	<0.001
First CK-MB positive***	403/1962 (20.5%)	354/491 (72.1%)	<0.001
First trop T positive****	700/1925 (36.4%)	372/434 (85.7%)	<0.001

Data are n/N (%) or mean (SD). TIMI=thrombolysis in myocardial infarction. ACT=activated clotting time. UFH=unfractionated heparin. PCI=percutaneous coronary intervention. CAG=coronary angiography. IABP=intra aortic balloon pump. MBG=myocardial blush grade. Hb=hemoglobin. CK=creatine kinase. CK-MB=creatine kinase myocardial band.

*=p for trend

** First CK positive= >200

*** First CK-MB positive= >6% of CK, when CK>200

**** First trop T positive= >0.05

Elevated LDH= LDH≥250 U/L

Table 3a: Clinical outcomes in patients with and without elevated LDH

Baseline	Normal LDH N=1962	Elevated LDH N=491	P value
Peak CK	1150 (447 – 2460)	1800 (763-3640)	<0.001
30 day Outcome			
Death	32/1907 (1.7%)	64/474 (13.5%)	<0.001
Recurrent MI	28/1907 (1.5%)	10/474 (2.1%)	0.319
Death, recurrent MI or stroke	63/1907 (3.3%)	74/474 (15.6%)	<0.001
Urgent TVR	57/1907 (3.0%)	27/474 (5.7%)	0.004
MACE	95/1907 (5.0%)	88/474 (18.6%)	<0.001
30 day Safety			
Major or minor bleeding*	51/1907 (2.7%)	37/474 (7.8%)	<0.001
Major bleeding*	24/1907 (1.3%)	17/474 (3.6%)	<0.001
Minor bleeding*	27/1907 (1.4%)	20/474 (4.2%)	<0.001
Stroke	8/1907 (0.4%)	3/474 (0.6%)	0.466
1 year Outcome			
Death	74/1694 (4.4%)	88/413 (21.3%)	<0.001
Recurrent MI	43/1694 (2.5%)	12/413 (2.9%)	0.675
Death and/or MI	111/1694 (6.6%)	97/413 (23.5%)	<0.001

Data are n/N (%) or median (IQR). CK=creatine kinase.

TVR=target vessel revascularization. MI=myocardial infarction. MACE=major adverse cardiac event. * Non CABG-related bleeding

Elevated LDH= LDH≥250 U/L

Table 3b: Clinical outcomes in patients with and without elevated LDH according from symptom onset (SO) to arrival PCI centre

	SO - arrival PCI centre > median			**SO - arrival PCI centre ≤** median		
	Normal LDH N=667	**Elevated LDH N=289**	**P value**	**Normal LDH N=860**	**Elevated LDH N=147**	**P value**
30 day Outcome						
Death	11/645 (1.7%)	34/282 (12.1%)	<0.001	14/837 (1.7%)	23/143 (16.1%)	<0.001
Recurrent MI	5/645 (0.8%)	4/282 (1.4%)	0.467	17/837 (2.0%)	5/143 (3.5%)	0.384
Death, recurrent MI or stroke	15/645 (2.3%)	37/282 (13.1%)	<0.001	30/837 (3.6%)	29/143 (20.3%)	<0.001
Urgent TVR	13/645 (2.0%)	15/282 (5.3%)	0.007	29/837 (3.5%)	10/143 (7.0%)	0.046
MACE	23/645 (3.6%)	46/282 (16.3%)	<0.001	49/837 (5.9%)	33/143 (23.1%)	<0.001
1 year Outcome						
Death	24/559 (4.3%)	50/242 (20.7%)	<0.001	37/726 (5.1%)	29/126 (23.0%)	<0.001
Recurrent MI	12/559 (2.1%)	6/122 (2.5%)	0.771	23/726 (3.2%)	4/126 (3.2%)	1.000
Death and/or MI	33/559 (5.9%)	54/242 (22.3%)	<0.001	58/726 (8.0%)	32/126 (25.4%)	<0.001

Median=150 minutes.

Data are n/N (%) or median (IQR). TVR=target vessel revascularization. MI=myocardial infarction. MACE=major adverse cardiac event.

Elevated LDH= LDH≥250 U/L. SO=symptom onset.

Table 4: Independent determinants of 30-day mortality

Univariate:

	Hazard rate	95% CI	P value
Age	1.07	[1.05 – 1.09]	<0.001
Female gender	1.21	[0.78 – 1.87]	0.395
Killip > 1	8.24	[5.45 – 12.46]	<0.001
Three vessel disease	2.87	[1.81 – 4.53]	<0.001
Diabetes Mellitus	1.75	[1.05 – 2.92]	0.032
Renal insufficiency	5.25	[3.52 – 7.84]	<0.001
Elevated LDH	8.51	[5.57 – 13.01]	<0.001
Anterior infarction	1.21	[0.76 – 1.91]	0.430
SO-arrival > 6 hrs	1.55	[0.93 – 2.59]	0.093

Multivariate:

	Hazard rate	95% CI	P value
Age	1.04	[1.02 – 1.07]	0.002
Female gender	0.59	[0.32 – 1.06]	0.076
Killip > 1	2.65	[1.47 – 4.76]	<0.001
Diabetes Mellitus	1.19	[0.61 – 2.34]	0.605
Renal insufficiency	2.20	[1.25 – 3.86]	0.006
Three vessel disease	1.82	[1.07 – 3.11]	0.028
Elevated LDH	6.28	[3.55 – 11.12]	<0.001
Anterior infarction	0.98	[0.58 – 1.66]	0.944
SO-arrival > 6 hrs	0.54	[0.26 – 1.12]	0.10

Elevated LDH= LDH≥250 U/L. SO=symptom onset.

Table 5: Independent determinants of 1-year mortality

Univariate:

	Hazard rate	95% CI	P value
Age	1.07	[1.06 – 1.09]	<0.001
Female gender	1.27	[0.91 – 1.77]	0.162
Killip > 1	5.85	[4.15 – 8.25]	<0.001
Three vessel disease	2.73	[1.93 – 3.87]	<0.001
Diabetes Mellitus	1.85	[1.25 – 2.73]	0.002
Renal insufficiency	4.15	[3.04 – 5.66]	<0.001
Elevated LDH	5.44	[3.99 – 7.41]	<0.001
Anterior infarction	1.19	[0.84 – 1.68]	0.329
SO-arrival > 6 hrs	1.61	[1.08 – 2.38]	0.018

Multivariate:

	Hazard rate	95% CI	P value
Age	1.06	[1.01 – 1.04]	0.001
Female gender	0.65	[0.43 – 0.99]	0.046
Killip > 1	2.42	[1.54 –3.80]	<0.001
Three vessel disease	2.04	[1.39 – 3.00]	<0.001
Diabetes Mellitus	1.28	[0.80 – 2.05]	0.309
Renal insufficiency	2.01	[1.35 – 3.01]	0.001
Elevated LDH	3.42	[2.33 – 5.01]	<0.001
SO-arrival > 6 hrs	0.85	[0.53– 1.39]	0.524

Elevated LDH= LDH≥250 U/L. SO=symptom onset.

Figure 1: Flow-chart of the study population. Elevated LDH= LDH≥250 U/L.

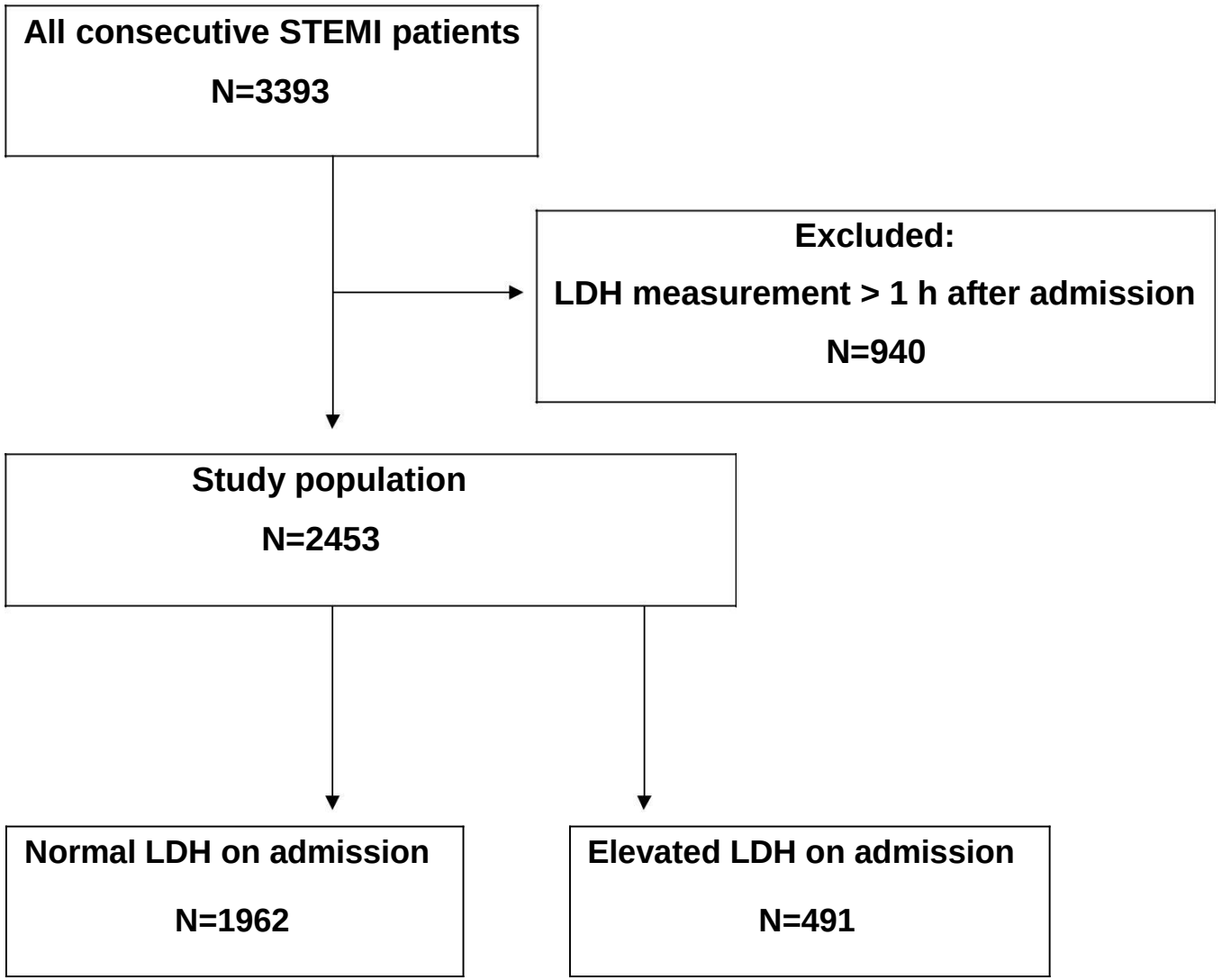
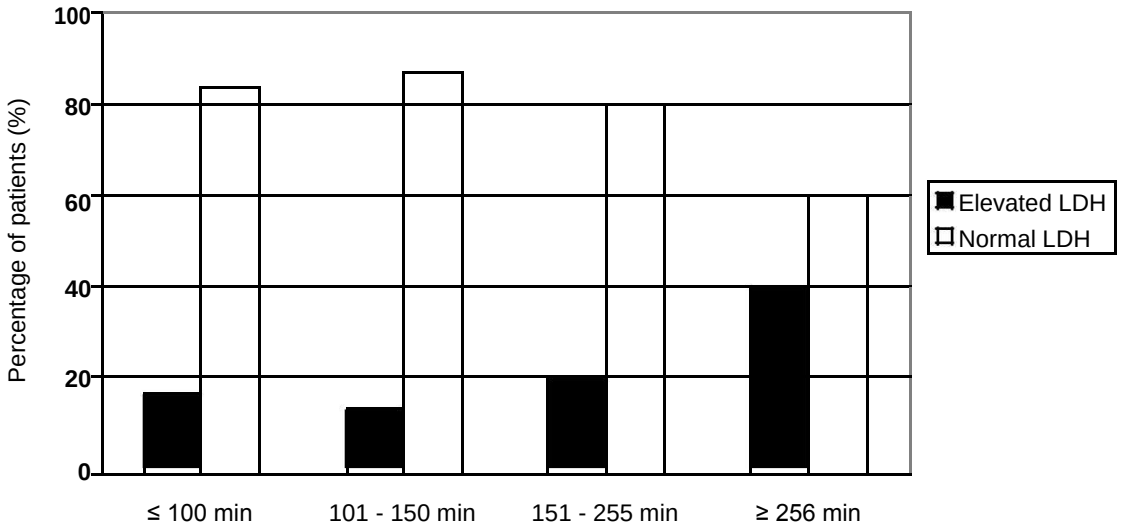
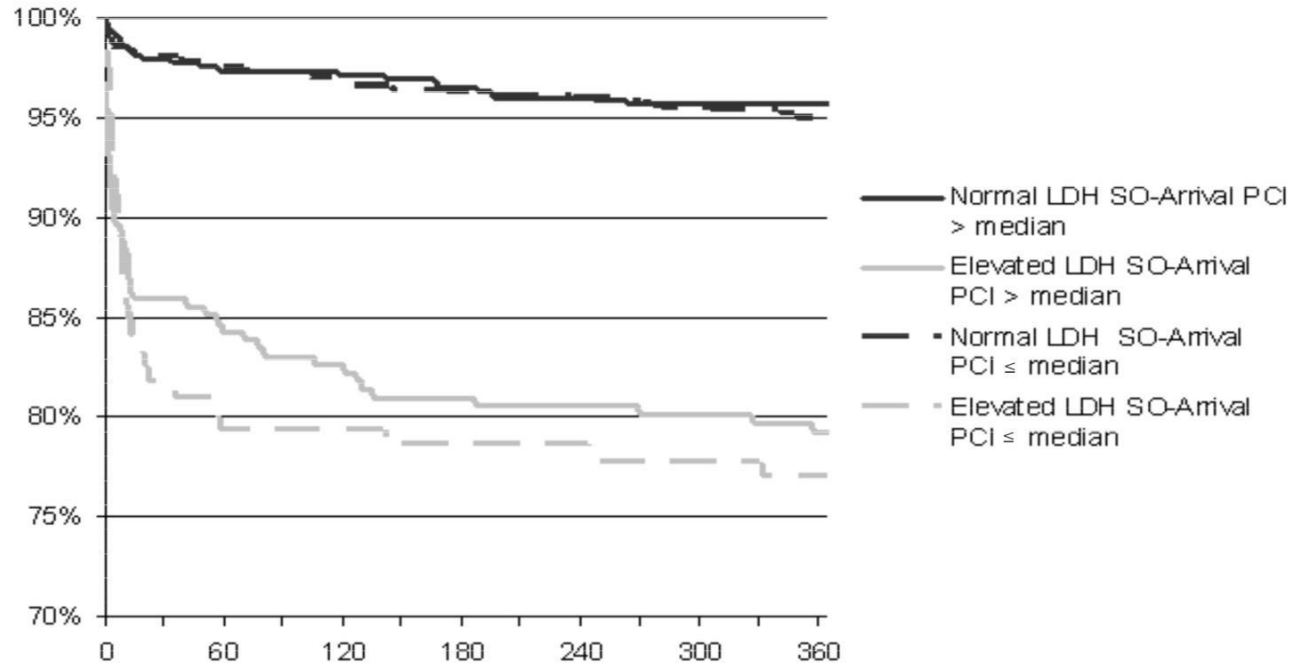


Figure 2: Distribution elevated/normal LDH on admission according to time from symptom onset to arrival PCI centre in quartiles



P for trend < 0.001

Figure 3: Time to event curves (Kaplan-Meier) for 1-year mortality in the 2 groups adjusted for symptom onset to arrival PCI centre >2 hours and 30 minutes (median)



Numbers at risk	0	60	120	180	240	300	360
SO-Arrival PCI > median							
Normal LDH	559	544	543	540	537	535	476
Elevated LDH	242	204	200	196	195	194	170
SO-Arrival PCI ≤ median							
Normal LDH	726	708	702	699	697	693	600
Elevated LDH	126	100	100	99	99	98	88

