# Rhabdomyolysis - a ten-year retrospective study of patients treated in a medical department

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# Abstract

Background: Rhabdomyolysis is a common and potentially life-threatening syndrome, with acute kidney injury (AKI) as a serious complication. There are only a few larger studies on the subject and there are no recent and relevant studies from Europe. Therefore, we did a ten-year retrospective study including all patients treated for rhabdomyolysis in a medical clinic, studying clinical characteristics, aetiologies, treatment, complications and mortality. Further, we studied correlations between CK, myoglobin and creatinine (as a marker of renal function and thereby AKI), and whether CK/myoglobin ratio could be a valuable tool in the diagnostics of this patient group.

Methods: The study included all patients treated for rhabdomyolysis at the Department of Medicine, Oslo University Hospital, Ulleval, from 2003 and until the end of 2012. Rhabdomyolysis was defined as serum CK values greater than 5 times the upper limit of normal.

Results: 341 patients met the inclusion criteria; 67% were males and median age was 54 years (range 17-99). AKI occurred among 51% and 10% were in need of dialysis. Mortality in the group as a whole was 4%. The most common aetiologies were immobilization (60%), prescription drugs (55%) and illicit drugs and/or alcohol (35%). Maximum serum CK and myoglobin correlated equally to creatinine values for the included patients. Logistic regression showed that myoglobin was better in predicting the development of AKI than CK. And CK/myoglobin ratio was a good predictor for AKI: lower values than 5.70 increased the likelihood of developing AKI, whereas higher values indicated that development of AKI was less likely.

Conclusions: AKI was a common complication among patients treated for rhabdomyolysis in our medical department, and nearly one out of five of those needed dialysis. Serum myoglobin was a better predictor for AKI than CK, and CK/myoglobin ratio could be useful to assess the likelihood of developing AKI.

Keywords: rhabdomyolysis; creatinine kinase; myoglobin; acute kidney injury; dialysis

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# 1 Background

Rhabdomyolysis is a common and potentially life-threatening syndrome characterised by muscle damage and breakdown of skeletal muscle with leakage of intracellular substances such as myoglobin and creatinine kinase (CK) into the circulation (1, 2). One of the most serious complications of rhabdomyolysis is acute kidney injury (AKI). Myoglobin plays a dominant role in the pathogenesis of rhabdomyolysis induced AKI (3, 4). Kidney failure ranges from 16.5 to 65% in different studies (5- 12). The aetiological spectrum of rhabdomyolysis is extensive, and in many cases multiple muscle insults are needed (1). Rhabdomyolysis can be divided into four main aetiological categories; direct or compression trauma, excessive muscular activity, hereditary enzyme disorders and other medical causes (13). The common denominators for all aetiologies are direct or indirect muscle damage and leakage of muscle constituents into the circulation. The typical triad of symptoms involves muscular pain, weakness and reddish-brown urine, although more than half of the patients do not report muscular symptoms (8).

There have been many reviews and some smaller retrospective cohort studies on the subject of rhabdomyolysis, but to date there are only two larger studies (5, 6). Comprehensive studies are lacking and there are no recent and relevant studies from Europe.

Our aim was to do a ten-year retrospective study on patients treated for rhabdomyolysis at The Department of Medicine, Oslo University Hospital, Ulleval, during the period from 2003 to the end of 2012. We wanted to study the incidence of clinical characteristics, different aetiologies, treatment, complications and mortality. Furthermore, we studied correlations between CK, myoglobin and creatinine (as a marker of renal function and thereby AKI) for the patients, and whether CK/myoglobin ratio could be a valuable tool in the diagnostics of this patient group.

# 2 Methods

## 2.1 Material

An increased level of serum CK is the diagnostic hallmark of rhabdomyolysis, and is commonly defined as serum CK values greater than 5 times the upper limit of normal (5, 8, 9, 11). The reference range varies with gender and age. For females the 5 times upper limit is 1050 U/L, for males in the age 18 - 49 years 2000 U/L and for males 49 years or older 1400 U/L (14). We used this definition of rhabdomyolysis in our study.

Inclusion criteria were all patients treated for rhabdomyolysis that had serum CK values greater than 5 times the upper limit of normal. CK is elevated in the first 12 hours after onset of muscle damage, the peak is observed during the first 3 days and is then declining in 3-5 days (1, 2, 13, 15- 17). Medical records of patients admitted to Oslo University Hospital, Ulleval, between January 2003 and December 2012 were reviewed and the following diagnoses included according to the International Classification of Diseases version 10 (ICD-10) (18): T79.6 Traumatic ischemia of muscle, M62.8 Other specified disorders of muscle and R82.1 Myoglobinuria. A manual search was done in addition to a search in the electronic journal system to make sure we had not missed any of the cases in the first review.

All trauma and surgical patients were excluded because they were not treated at the medical department. However, patients treated with cardiac pulmonary resuscitation (CPR) because of cardiac arrest were included as long as they otherwise fulfilled the criteria for rhabdomyolysis. The same was true for patients with myocardial infarction or stroke. All had to have a concomitant aetiology of rhabdomyolysis to get included.

We used the medical journals to find the information needed for this study. For all the patients we recorded gender, age, days of hospitalization, treatment level and rhabdomyolysis as main or second diagnosis.

More than one aetiology could be registered per patient. Prolonged compression during immobilization was registered if the patients were found lying on the floor unable to move, and had most likely been there for several hours. For prescription drugs we did a search in the

Norwegian Pharmaceutical Product Compendium on medication associated with rhabdomyolysis (19). We also registered medications that have been associated with rhabdomyolysis in other studies/ reports (5, 13, 17). Use of illicit drugs and/ or alcohol was registered if used within a day before admission to hospital or if there was a history of drug abuse or alcoholism. Acute infections have been reported to be associated with rhabdomyolysis, both bacterial and viral (9, 20). Infections were registered based on clinical evaluation/ laboratory results. Dehydration was recorded if the treating doctor had noted it in the journal and/or it was coded for in the discharge papers. Exercise and seizures were registered if they preceded the episode of rhabdomyolysis, and seizures had to have been observed by companions. Patients with the diagnosis diabetes were registered, and general electrolyte disorders or metabolic disorders were registered as "Other metabolic disorders", and included: hypokalaemia (potassium < 3,6 mmol/L), hypo- and hypernatremia (sodium < 137 mmol/L and > 145 mmol/L), hypocalcaemia (calcium < 2,15 mmol/L), hypophosphatemia (phosphate < 0,75 mmol/L (male) and < 0,85 mmol/L (female)) and diabetic ketoacidosis (glucose > 14 mmol/L, arterial pH< 7,3, serum bicarbonate < 18 mEq/L, serum and urine ketone) (14, 21). Hyperthermia/ hypothermia was defined as a temperature above 38/ below 35 degrees. Known muscle diseases or muscle diseases detected when admitted were recorded. We subdivided muscle diseases into metabolic myopathy, muscle dystrophy/ other hereditary muscle diseases, myositis or myopathy if no other diagnosis fit. If there were other aetiologies that could explain the high serum CK this was recorded as others, and the aetiology were noted. If no aetiologies were found the case was registered as idiopathic.

Treatment received was recorded and included fluid resuscitation with isotonic saline or other isotonic fluid, urine alkalinisation with sodium bicarbonate (forced alkaline diuresis), diuretics and dialysis. A patient could receive more than one form of treatment. For the patients in dialysis it were noted if there were used intermittent haemodialysis, continuous haemodialysis or peritoneal dialysis. One patient were undergoing dialysis because of lithium intoxication and one because of end stage kidney disease, they were both excluded.

Complications and mortality was recorded. AKI was defined as an increase in serum creatinine above the upper limit of normal range as in a previous study (5), female >90 μmol/L, and men >105 μmol/L (14). Maximum serum creatinine values were registered, and

estimated glomerular filtration rate (eGFR) was calculated based on age and gender (22, 23). Normal range for eGFR is above 90 (mL/min/1.73m2). 19 patients had a known chronic kidney disease before hospitalization; they were only registered with AKI if their renal disease were worsened. Another important complication in rhabdomyolysis is electrolyte disorders like hyperkalaemia (> 4.6 mmol/L) and hypocalcaemia (< 2.15 mmol/L) (14). Based on lab values maximum potassium and minimum calcium were registered, and the number of patients in need of electrolyte supplements were noted. We noted if the patients got cardiac disturbance/ arrhythmia on Electrocardiogram (ECG) because of the electrolyte disorders. We also registered the total number of patients who got compartment syndrome and if they were in need of a surgical fasciotomy. The diagnosis compartment syndrome was based on an orthopaedic surgeons assessment. The patients who died during hospitalization were registered and the cause of death noted.

For all patients the maximum level of serum CK was recorded. Serum myoglobin, electromyography (EMG)/ electroneurography (ENG) and muscle biopsies were recorded when available.

## 2.2 Ethics

The Ombudsman at Oslo University Hospital granted approval for this study, and the need for informed consent were waived. All data were unidentified before analysis.

## 2.3 Statistical analysis

Statistical analyses were performed using SPSS (International Business Machines Corp, NY), version 22.0. Categorical variables were described by frequency distribution. Continuous variables were expressed as mean (SD) or median and interquartile range as appropriate. Chi square tests were used to assess differences in proportions for categorical data, and the t-test was used for continuous variables if they were normally distributed. Pearson correlation test was used to evaluate the relationship between CK, myoglobin and creatinine. Logistic regression analyses were used to investigate whether CK, myoglobin and/or CK/myoglobin ratio were better predictors for AKI (the dependent variable). Here, a Forced Entry Method was used. Visual binning was used to divide the study sample into two groups: low CK/myoglobin ratio (50%) and high CK/myoglobin ratio (50%). Chi square test were used to

compare the number of AKI in the two groups. p-values <0.05 were considered statistically significant.

# 3 Results

## 3.1 Patients

Totally 341 patients were included in the study: 227 males (67%) and 114 females (33%), see table 1. Median age was 54 years (range 17- 99). For males the median age was 50 years and for females 65 years ($p<0.001$). 109 patients (32%) had rhabdomyolysis as their main diagnosis and 232 (68%) had it as an additional diagnosis. There were 33 patients (10%) who were hospitalized for one day or less, 29 (9%) for two days and 279 (82%) for thee days or more. 196 patients (58%) were treated in a general ward, whereas, 41 (12%) were at the ICU for one day or less, 21 (6%) were at the ICU for two days and 83 (24%) for three days or more.

## 3.2 Aetiology

The three most common aetiological causes of rhabdomyolysis in our patient cohort were immobilization, prescription drugs and illicit drugs/alcohol (table 2). Immobilization was the largest group and consisted of 204 patients (60%). The patients in this group were often intoxicated and had been in the same position for a long time, or they were elderly who had fallen at home and were unable to get up. In the last group there was often an infection, stroke or another concomitant disease, and they were often dehydrated, had a high temperature and had a long list of prescription drugs. In only 8 cases (2%) no other concomitant aetiologies besides immobilization was registered.

Prescription drugs were the second largest group in our cohort with a total of 186 patients (55%). The list of drugs associated with rhabdomyolysis was extensive and included among others selective serotonin reuptake inhibitors (SSRI) and other antidepressants, diuretics, antipsychotics and statins (table 3). Use of antidepressants and diuretics were registered in 52 (15%) and 47 patients (14%), respectively, and one patient in each group had this as their main aetiological reason. 42 patients (12%) were using antipsychotics when admitted, and it was considered the main reason in four cases. 41 patients (12%) were using statins, for eleven patients this was considered the main reason and for three statins in combination with respectively antipsychotic, cyclosporine and erythromycin were considered the main reasons.

The third largest aetiological cause was the group with a positive history of illicit drugs and/ or alcohol, and included 118 cases (35%). 72 of the patients in this group were admitted due to intoxication, illicit drugs/ alcohol were the main reasons in 51 cases and prescription drugs were the main reason in eleven cases. Only 16 patients were admitted with intoxication without concomitant use of illicit drugs/ alcohol, here immobilization, seizures or hypothermia were the main reasons for rhabdomyolysis. Only nine patients had illicit drugs/ alcohol as their only aetiological reason.

Totally 76 patients (22%) had an acute infection when admitted. 65 patients (19%) had an bacterial infection with respectively pneumonia, sepsis and urinary tract infection as the most common groups (11%, 4%, 4%). Two patients had erysipelas and one had dengue fever. Eleven patients (3%) were registered with a viral infection: four of them had a Human Deficiency Virus (HIV) infection, three had a viral upper airway infection, two had influenza, one had a Herpes Zoster Infection and one had viral encephalitis of unknown origin.

Some of the other causes of rhabdomyolysis in this cohort were dehydration, which included 72 (21%) patients. Dehydration was always concomitant with other aetiologies. The group with diabetes and general metabolic/ electrolyte disorders included 32 (9%) and 27 patients (8%), respectively. Exercise was registered as a cause in 30 patients (9%), and for 25 patients (7%) there were reported seizures. Hyperthermia/ hypothermia were found in 24 (7%) and 16 patients (5%), respectively. Twelve patients (4%) had a primary muscle disease. Six of them had a metabolic myopathy, five were defined as myositis and one as myopathy. No patients with muscle dystrophy/ other hereditary muscle diseases forfilled the diagnostic requirements for rhabdomyolysis in this study. Two patients were admitted several times, both of them were believed to have a metabolic myopathy. One was later diagnosed using muscle biopsy, the other never showed up for his appointments. In the group “Other aetiologies”, was among other eight cases of psycomotoric agitation and three of them had antipsychotic medication as a concomitant aetiology.

A total of six cases of cardiac arrest were included in the study. One collapsed during a long cycling race, and the extensive exercise was considered the main reason for the development of rhabdomyolysis. For the five others there were illicit drug or alcohol intoxication that were the main reasons, for all of them there had been a period of immobilisation and for one hypothermia was a contributing factor.

Multiple aetiologies were registered in 279 patients (82%) included in this study. And only 62 patients (18%) had a single aetiological cause. In all groups of aetiologies, more male than female were registered, except in the groups with seizures and metabolic disorders.

## 3.3 Treatment

After the diagnosis of rhabdomyolysis were established, the patients were treated with fluid replacement therapy (92%), urine alkalization with sodium bicarbonate (51%) and/or diuretics (30%), see table 4. The treatment guidance at Ulleval when it comes to administration of bicarbonate (forced alkaline diuresis) is to start at CK > 10000 U/L. Of 208 patients with CK more than 10000 U/L - 164 (79%) was receiving this treatment, and nine patients with CK below 10000 U/L were treated with bicarbonate. 35 patients (10%) were in need of dialysis, and all of them got haemodialysis except one who got peritoneal dialysis. All of the patients treated with dialysis had AKI. Median days in dialysis were 8, range 1-29 days.

## 3.4 Complications and mortality

AKI occurred in 173 patients (51%), see table 5. Average serum creatinine in the patients with AKI was 333 μmol/L, and 93% of them had eGFR below 60 and 7% had eGFR below 90. The group consisted of 116 males (67%) and 57 females (33%), $p<0.001$. Median age was 60 years, 59 and 65 years for males and females respectively (n. s.). Immobilization, prescription drugs and illicit drugs/alcohol were also the most common aetiologies when it came to AKI with respectively 36, 28 and 19%. AKI was seen in all the aetiological groups.

Another important complication was hyperkalaemia and hypocalcaemia, which affected respectively 158 (46%) and 187 (54%) patients. Average maximum potassium was 4.8 mmol/l and average minimum calcium was 2.0 mmol/l, both just over/ under the reference level. 15 patients (4%) were registered with cardiac arrhythmias because of electrolyte disturbance. In those with cardiac arrhythmias maximum potassium was 6.6 mmol/l in average and minimum calcium was 1.7 mmol/l in average, so potassium were higher and calcium were lower than in the cohort as a general. 71 patients (21%) were in need of electrolyte supplements because of different electrolyte disorders.

33 patients (10%) got compartment syndrome. For seven of those, surgical intervention with fasciotomy was indicated. For 24 patients surgical intervention with fasciotomy was not indicated due to established muscle death. It was here considered that the compartment syndrome had been there for so long that the muscle already was dead. The risk of infection due to an operation was considered greater than the benefit of an operation.

A total of twelve patients (4%) died during hospitalization. Eight of those were elderly who had been found immobilized at home, two were admitted because of intoxication and two were critical ill because of an acute bacterial infection. A short case history is given in table 6. The mortality rate in the patient group with AKI was 6%.

## 3.5 Serum creatinine kinase (CK), myoglobin and AKI

Average serum CK in the whole cohort was 33454 U/L (range 1203 - 563700 U/L), and average serum myoglobin was 10649 ng/ml (range 26 - 228009 ng/mL). In the patients with AKI, average serum CK and myoglobin were respectively 42776 U/L and 16568 ng/mL - both higher than in the total cohort. The correlation between maximum CK values and maximum creatinine (as a marker of renal function and thereby AKI) was good for patients with rhabdomyolysis (figure 1a), with a Pearson correlations coefficient of 0.426. The correlation between maximum myoglobin and creatinine was equally good (figure 1b), with a Pearson coefficient of 0.433.

Logistic regression showed that maximum CK was a significant predictor of AKI ($p=0.004$). However, when both CK and myoglobin was included in the analyses, only maximum myoglobin remained as a predictor of AKI, se table 7. Also, the CK/myoglobin ratio was a good predictor of AKI; logistic regression showed that a lower ratio increased the likelihood of AKI (Odds ratio 0.984, $p =0.014$). Visual binning showed that dividing the sample into a high and low ratio gave a cut off at 50% at 5.70; i.e. lower ratio than 5.70 increased the likelihood that the patient developed AKI, whereas higher values than 5.70 indicated that this was less likely ($p<0.001$).

Average serum CK and myoglobin in the group who died was respectively 27680 U/L and 11064 ng/mL. CK was lower than in the total cohort but myoglobin was higher.

## 3.6 EMG/ ENG and Muscle biopsy

EMG/ ENG was done in 17 patients (5%). For one the EMG/ ENG was inconclusive, five showed myopathy, two showed neuron damage because of immobility/ compression, three showed neuron damage because of compartment syndrome and six were negative. Muscle biopsy was taken in seven patients (2%), one showed myositis, three showed a general myopathy and three were negative.

# 4 Discussion

Immobilization was by far the most common aetiological factor for rhabdomyolysis in our retrospective cohort study. Half of the patients developed AKI during hospitalization. Both maximum serum CK and myoglobin correlated well with creatinine and thereby AKI. Interestingly, we found that serum myoglobin was a better predictor for AKI than serum CK, and indications that CK/ myoglobin ratio can be a useful clinical predictor for AKI, as a low ratio increases the risk for AKI.

There has been several smaller retrospective studies on rhabdomyolysis (7- 10, 12), but only two larger population studies has been done on this subject: the American retrospective study from 2005 by Melli et al. (5), including 475 hospitalized patients with CK more than 975 U/L, and the more recently larger American retrospective study by McMahon et al. (6), including 2371 patients with CK more than 5000 U/L. The last one registered the frequency of different aetiologies, but their objective was to develop a risk prediction tool to identify patients at risk of renal replacement therapy (RRT) and mortality.

We registered 24 different aetiologies in our study; a broader spectrum of causes than in previous studies. The most likely cause for this is that we chose to register more than one aetiology per patient instead of only the main aetiology. This gives a better answer to the actual aetiological frequency in rhabdomyolysis, but has only been done in two smaller studies before (8, 10). The disadvantage is that all aetiologies are weighted equally, although their relative importance probably varies.

Immobilization was in our study the largest aetiological cause and included 60% of the patients. This is a much higher frequency than previously reported. Immobilization was also the most common medical aetiology in the study by McMahon et al. (6), but the frequency reported there was only 18%. And in the study by Melli et al. (5) was it reported as the eight larges group with a 2% frequency. A possible reason for the lower frequency reported in these two studies, is that they registered only the main aetiology. In the current study the frequency percentage will necessarily be higher for some groups, especially for the groups that are often considered contributors to rhabdomyolysis but not the main cause, and maybe that applies to immobilization. In support of this, only eight cases of immobilization were

registered as the only aetiological reason in our study. But, the registration of more than one aetiology per patient cannot explain the whole difference between previous studies and the present, as the reported frequency was also much lower (19 and 39%) in two studies that registered more than one aetiology per patient (8, 10). Nor could patient characteristics explain the large difference. In ours, like in previous studies, males were predominantly affected and no major difference in age composition is seen (5- 8, 10- 12).

The second largest aetiological cause in the current study was prescription drugs, affecting 55% of the patients. There have been many reports on prescription drugs associated with rhabdomyolysis, but few studies have been done on the actual frequency (5, 13, 17). The list of drugs associated with rhabdomyolysis was extensive in ours as in a previous study (5). Antidepressants, diuretics, antipsychotics and statins were the most frequent medications in our patient cohort; this was also true in the previous study by Melli et al. (5) except for diuretics, which was not reported at all. But the frequency was higher in our study with 15% reported cases of antidepressants and 12% for antipsychotics and statins each, compared to respectively 3, 8 and 4% in their study. Drug induced rhabdomyolysis can be divided into a primary and secondary myotoxic effect, where the primary is due to direct myotoxic insults to the skeletal myocyte and the secondary is due to predisposing risk factors such as immobilization etc. (24). Many of the registered prescription drugs are commonly used and it is difficult to distinguish the contributing effect of each of them. Ideally there should have been a control group to say something more precise about the association between prescription drugs and rhabdomyolysis. Also the accuracy of calling them aetiological factors can be discussed, since their contributing effect are not known. More studies have to be done on this subject.

The third largest group in our study, including 35% of the patients, was the group consisting of illicit drugs and/or alcohol. This is consistent with previous studies (5, 7- 10). Interestingly in the study by McMahon et al. (6), which is the largest cohort study on rhabdomyolysis to date, the only implicated illicit drug were cocaine with a frequency on 0.4%. No other illicit drugs or alcohol were reported. Since illicit drugs/alcohol is a widely reported cause in rhabdomyolysis, a likely explanation could be that other aetiologies have been considered more important and thereby registered as the main one. Only 3% of the patients in our cohort had illicit drugs/ alcohol reported as their only aetiological reason.

Unlike the results in our study, muscle diseases and neuroleptic malignant syndrome (NMS) are important aetiological factors in the study by Melli et al. (5). In our study no patients with NMS was registered and only 4% of the patients had a primary muscle disease. In the present study only 5% of the patients got EMG/ ENG and in only 2% a muscle biopsy was performed, this number was much higher in the study by Melli at al. (5). Could it be that because patients with rhabdomyolysis often have multiple aetiologies, that we are overlooking a primary muscle disease as a contributing factor? The investigation for uncovering a primary muscle disease could probably be more systematic, and the threshold for ordering EMG/ ENG and muscle biopsies might be lower for patients with rhabdomyolysis.

The aetiological spectrum of rhabdomyolysis is extensive and in many cases multiple muscle insults are needed (1). In support of this only 18% of the patients in our study had a single aetiological factor and in entire 82% multiple aetiological factors were found. This is higher than in previous studies where the presence of multiple concomitant aetiologies has ranged from 37- 60% (5, 8, 10).

AKI is the most serious complication in rhabdomyolysis and ranges from 16.5 to 65% in previous studies (5- 12). A possible reason for the wide range can be the different definitions of AKI, different patient cohorts and different inclusion criteria in different studies. In the current study AKI developed in 51% of the patients. This is quite similar to the studies by Melli et al. (5) and McMahon et al. (6), where respectively 46 and 48% developed AKI. We had the same inclusion criteria and the same definition of AKI as in the study by Melli et al. (5) so the results between our studies should be comparable. As a note, it is quite serious that half of the patients with rhabdomyolysis develop AKI, and it shows that rhabdomyolysis is an important syndrome.

Mortality ranges from 3 to 46% in different studies (5- 10, 12). The possible reasons for this wide range is the same as for the wide range in AKI discussed in the previous section. In the current study 4% of the patients with rhabdomyolysis died. This is quite similar as in the study by Melli et al. (5), where 3.4% of the patient died. In the larger study by McMahon et al. (6) the rate of mortality was found to be 14.1%. This study included a high number of patients, but unlike our study and the study by Melli et al. (5) they included only patients with CK more than 5000 U/L, so their patients had probably a more severe rhabdomyolysis and

that could explain some of the difference. In our study the mortality in the group registered with AKI was 6%, which is slightly higher than in the cohort as a general, but lower than expected. Also in a previous study no correlation has been found between AKI and death (5). A possible explanation could be that other factors than AKI are important for mortality. In support of this, the study by McMahon et al. (6) found that age, female sex, cause of rhabdomyolysis and values of initial creatinine, CK, phosphate, calcium and bicarbonate were independent predictors for mortality (and RRT).

Electrolyte derangements are a common complication in rhabdomyolysis, especially hyperkalaemia and hypokalaemia. This was also a frequent complication in our study and 46% was registered with hyperkalaemia and 54% with hypocalcaemia, which is higher than previously reported. In two previous studies this was reported to affect respectively 8 to 13% and 21 to 41% (7, 8). A possible reason is that they had a higher/ lower definition of hyperkalaemia/ hypocalcaemia (potassium > 5.5 mmol/L, calcium < 2.0 mmol/L) than in the current study (potassium > 4.6 mmol/L, calcium < 2.15 mmol/L). In the current study 4% developed cardiac arrhythmias because of electrolyte disturbance; in this group maximum potassium was in average 6.6 mmol/L and minimum calcium was 1.7 mmol/L this is higher/ lower than in the cohort as a general (4.8 mmol/L, 2.0 mmol/L).

There is a lack of evidence for the best treatment of rhabdomyolysis. To date there are no randomised controlled trials who look at treatments for rhabdomyolysis and most evidence is based up on retrospective studies, case reports and animal models (1). In the current study 10% of the patients got compartment syndrome and for 2% of these surgical fasciotomy were indicated. Other forms of treatment that were given were isotonic fluids, urine alkalization with sodium bicarbonate, diuretics and dialysis. Our treatment guidance at Ulleval when it comes to administration of sodium bicarbonate (forced alkaline diuresis) is CK > 10000 U/L. Of 208 patients with CK > 10000 U/L, only 79% were receiving bicarbonate. However, nine patients with CK below 10000 U/L were receiving the treatment. The reason for this is not known, and it may seem that the treatment given is not only dependent on the treatment guidance but also depends on the treating physician's assessment. In our study 11% of the patients with AKI were in need of dialysis. Interestingly, in the study by McMahon et al. (6), only 8% were in need of dialysis although they probably had a patient cohort with more

severe rhabdomyolysis as discussed in a previous section. Perhaps this can be explained by different indications for when dialysis is started in different hospitals.

In the current study the correlation between maximum serum CK, myoglobin and creatinine was good for patients with rhabdomyolysis. Maximum CK was a significant predictor of AKI, but when both CK and myoglobin was included in the analyses, only maximum myoglobin remained as a predictor of AKI. It was found that CK/myoglobin ratio was a good predictor for the development of AKI - a lower ratio increased the likelihood that the patient developed AKI. Correlation between CK and AKI (peak creatinine) has been shown in some previous studies (5, 10, 12). Other studies report a weak (7, 11), or no correlation (8) between serum CK and AKI. Few studies have looked at the correlation between myoglobin and AKI, although serum myoglobin plays a dominant role in the pathogenesis of rhabdomyolysis induced AKI (3, 4). In rhabdomyolysis the level of myoglobin in serum increases within 1-3 days, reaches its peak in 8 - 12 hours and then returns to normal within 24 hours after the onset of the muscle injury (2). Serum myoglobin usually increases before an increase in serum CK, but because myoglobin has a short half- life (2-4h) it has not been considered an important marker and serum CK has been the hallmark of rhabdomyolysis (half-life of 1.5 days) (1, 2, 13, 16). Similar to our study, a small prospective study from Japan showed that peak myoglobin could be a better predictor for AKI than serum CK (25). As a note, in the current study serum myoglobin was often taken after the first blood samples had shown an increased CK and because myoglobin has a short half-life, the peak myoglobin value registered was probably too low. Also, myoglobin was not always taken and we had 37% missing variables, so the results must be interpreted with caution. To give a better answer to whether or not serum myoglobin is a good predictor for rhabdomyolysis it must be taken as son as possible after admission.

The current study and its design gives an overview of the clinical characteristics, aetiologies, treatment, complications and mortality and it gives probably a more nuanced view of the actual frequency of different aetiologies causing rhabdomyolysis than previous series, which only registered the main causes. But there are several limitations in this study. First, it is a small retrospective study so larger studies is required to say anything more definite about correlations between serum CK, myoglobin and AKI, and whether or not CK/myoglobin ratio could be a valuable tool in the diagnostics of this patient group. Second, Norway is quite homogeneous, but the population in Oslo is slightly different in terms of a higher number of

immigrants and substance abusers, so the frequency of some of the aetiologies may differ from the rest of the country. Third, the number of patients included in the study and the results may have been different if we had included the whole hospital. Trauma has in previous studies been an important aetiological reason for rhabdomyolysis (5- 8, 10). Forth, registering of illicit drugs/alcohol was based on the medical history. This dependent on whether or not the treating physicians asked about it/ brought it up and whether or not the patients were willing to admit it. The frequency was most likely higher than stated. And last, in the logistic regression analysis there was a possible multicollinearity between the variables so the results must be interpreted with caution.

In the future, larger prospective studies are required to assess the correlation between serum CK, myoglobin and AKI. Also, more studies have to be done to evaluate whether or not CK/myoglobin ratio could be a good predictor for the development of AKI, and if serum myoglobin is a better predictor for AKI than serum CK.

# 5 Conclusions

Immobilization, prescription drugs and illegal drugs/alcohol were the most common causes of rhabdomyolysis in our retrospective cohort study. AKI was a frequent complication, affecting half of the patients treated for rhabdomyolysis. Nearly one out of five of those with AKI were in need of dialysis. Serum myoglobin was a better predictor for AKI than CK, and CK/myoglobin ratio may be a valuable tool in the assessment of patients with rhabdomyolysis, as a low ratio increases the likelihood of developing AKI.

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# Tables and figures

**Table 1.** Patient characteristics for 341 patients in a 10-year cohort of patients treated for rhabdomyolysis. Gender is estimated based on the total cohort (n = 341)

| **Gender** | **Male**<br>**No. (%)** | **Female**<br>**No. (%)** | **Total**<br>**No. (%)** |
|---|---|---|---|
| | 227 (67) | 114 (33) | 341 (100) |
| **Median age** | 50 | 65 | 56 |
| **Rhabdomyolysis - main diagnosis** | 79 (23) | 30 (9) | 109 (32%) |
| **Rhabdomyolysis - second diagnosis** | 148 (43) | 84 (25) | 232 (68%) |
| **Days in hospital** | | | |
| 1 | 26 (8) | 7 (2) | 33 (10%) |
| 2 | 19 (6) | 10 (3) | 29 (9%) |
| 3 or more | 182 (53) | 97 (28) | 279 (82%) |
| **Treatment level** | | | |
| General ward | 131 (38) | 65 (19) | 196 (58%) |
| ICU- 1 day | 28 (8) | 13 (4) | 41 (12%) |
| ICU- 2 days | 16 (5) | 5 (1) | 21 (6%) |
| ICU- 3 days or more | 52 (15) | 31 (9) | 83 (24%) |

**Table 2.** Aetiologies for 341 hospitalized patients admitted with rhabdomyolysis. More than one aetiology could be registered per patient. Percentages of AKI were based on the total cohort (n =341).

| Aetiology | Males n=227 % | Females n=114 % | Total n=341 n(%) | AKI n=341 % |
|---|---|---|---|---|
| Immobilization | 38 | 22 | 204 (60) | 36 |
| Prescription drugs* | 33 | 21 | 186(55) | 28 |
| Alcohol and/ or Illegal drugs** | | | | |
| Total | 25 | 10 | 118 (35) | 19 |
| Alcohol | 9 | 6 | 51 (15) | 9 |
| Polydrug abuse | 10 | 2 | 41 (12) | 7 |
| Heroin | 4 | 2 | 20 (6) | 3 |
| Amphetamine | 1 | 0 | 5 (1) | 0.6 |
| GHB | 0.3 | 0 | 1 (0.3) | 0.3 |
| Infection | 13 | 10 | 76 (22) | 12 |
| Dehydration | 14 | 7 | 72 (21) | 13 |
| Diabetes | 6 | 3 | 32 (9) | 5 |
| Exercise | 8 | 1 | 30 (9) | 2 |
| Metabolic disorder | 3 | 5 | 27 (8) | 5 |
| Seizures | 4 | 4 | 25 (7) | 3 |
| Hyperthermia | 4 | 3 | 24 (7) | 4 |
| Hypothermia | 4 | 1 | 16 (5) | 4 |
| Primary muscle disease*** | 3 | 0.3 | 12 (4) | 0.6 |
| Metabolic myopathy | 2 | 0 | 6 (2) | 0 |
| Myositis | 1 | 0 | 5 (1) | 0.3 |
| Myopathy | 0 | 0.3 | 1 (0.3) | 0.3 |
| Other aetiologies**** | 6 | 3 | 31 (9) | 5 |
| Idiopathic | 1 | 0 | 3 (1) | 0.3 |

* For prescription drugs se table 3.

** Cocaine and ecstasy were checked for, but were not found among the cohort according to medical journals.

*** Muscle dystrophies and other hereditary muscle diseases were checked for but not found.

**** Other aetiologies: Psychomotoric agitation (8 patients), cardiac arrest (6 patients), fall from own height (5 patients), burns (3 patients), high voltage injury (2 patients), anabolic steroids (2 patients), frostbite (1 patient), ICU- myopathy (1 patient), sickle cell crisis (1 patient), serotonin syndrome (1 patient) and Viper venom (1 patient).

**Table 3.** Prescription drugs used by patients treated for rhabdomyolysis. Percentages of AKI were estimated based on the total cohort (n = 341).

| Prescription Drugs | Total No. (%) | AKI % |
|---|---|---|
| Selective Serotonin Reuptake Inhibitors (SSRIs) and other antidepressants | 52 (15) | 9 |
| Diuretics | 47 (14) | 9 |
| Antipsychotics | 42 (12) | 7 |
| Statins | 41 (12) | 6 |
| Angiotensin II receptor blockers | 35 (10) | 6 |
| Benzodiazepines | 34 (10) | 4 |
| Antiepileptics | 31 (9) | 4 |
| Antihistamines | 15 (4) | 3 |
| Immunosuppressive drugs | 7 (2) | 0 |
| HIV medication* | 6 (2) | 0.6 |
| Omeprazole | 6 (2) | 1 |
| Corticosteroids | 6 (2) | 0.9 |
| Antibacterial (Bactrim, fucidin, macrolid, cubicin, clacid) | 5 (1) | 0.6 |
| Anti-Parkinson drugs | 5 (1) | 0.6 |
| Lithium | 2 (0.6) | 0.6 |
| Theophylline | 1 (0.3) | 0 |
| Luteinizing hormone-releasing hormone agonist | 1 (0.3) | 0.3 |

* HIV medication = antiviral HIV medications and protease inhibitors.

Antiviral drugs hepatitis B and C, Colchicine, Amiodarone, Amphotericin B, Quinidine, Barbiturates, Anaesthetics and chemotherapeutic drugs were checked for, but were not found among the cohort.

**Table 4.** Treatment received during hospital stay for patients treated for rhabdomyolysis in a medical department (n=341). Each patient could receive more than one form of treatment.

| Treatment | Male % | Female % | Total No. (%) |
|---|---|---|---|
| Isotonic fluids | 61 | 31 | 313 (92) |
| Urine alkalinisation (with sodium bicarbonate) | 37 | 14 | 173 (51) |
| Diuretics | 21 | 10 | 103 (30) |
| Electrolyte supplements | 12 | 9 | 71 (21) |
| Dialysis | 8 | 3 | 35 (10) |
| Intermittent haemodialysis | 6 | 2 | 27 (8) |
| Combination of intermittent and continuous haemodialysis | 1 | 0.6 | 6 (2) |
| Continuous haemodialysis | 0.3 | 0 | 1 (0.3) |
| Peritoneal dialysis | 0.3 | 0 | 1 (0.3) |

**Table 5**. Complications and mortality for patients treated for rhabdomyolysis (n=341).

| Complications | Male n=227 % | Female n=114 % | Total n=341 n (%) |
|---|---|---|---|
| Hypocalcaemia | 39 | 16 | 187 (54) |
| Acute kidney injury (AKI) | 34 | 17 | 173 (51) |
| Hyperkalaemia | 33 | 13 | 158 (46) |
| Compartment syndrome | 7 | 3 | 33 (10) |
| Fasciotomy | 1 | 0.6 | 7 (2) |
| Cardiac arrhythmia | 4 | 0.6 | 15 (4) |
| Death | 3 | 0.9 | 12 (4) |

**Table 6.** Short case history and course in the twelve cases of rhabdomyolysis that resulted in death.

| Gender and age | Case history and course of disease. | CK U/l |
|---|---|---|
| **F, 92** | Extensive cerebral infarction. Fall at home, immobilized. Unresponsive at admission. Died after 7 days. | 10634 |
| **M, 87** | Influenza. Fall at home, immobilized. Aspiration pneumonia. ARDS. Died after 7 days. | 9804 |
| **M, 91** | Fallen at home, immobilized. Resuscitated with iv fluid- got pulmonary oedema. Aspiration pneumonia. Died after 8 days. | 5423 |
| **M, 63** | Pneumonia. Critically ill at admission. Respirator. ARDS. Statin + erythromycin interaction gave critical illness myopathy. AKI. Continuous haemodialysis. Multi-organ failure. Died after 20 days. | 153000 |
| **M, 28** | Intoxication. Comatose. Immobilized. Aspiration pneumonia, pneumothorax. Hypoxic brain damage on CT caput. AKI. Intermittent haemodialysis. Herniation during dialysis. Died after 12 days. | 69000 |
| **F, 87** | Fallen at home, immobilized for days. AKI. Sepsis. Died after one day. | 14200 |
| **M, 83** | Urosepsis. ARDS. CPAP. Developed pulmonary oedema, not responsive to treatment. Died after 6 days. | 17800 |
| **M, 83** | Fall at home, immobilized. Unresponsive at admission. Extensive cerebral bleeding. Died after one day. | 13660 |
| **M, 87** | Fall at home, immobilized. Pressure ulcers. Extensive cerebral infarctions. Died after 15 days. | 8911 |
| **M, 29** | Intoxication. Cardiac arrest. CPR. Unresponsive. Treated with hypothermia. Respirator. Multi- organ failure. Died after three days. | 23900 |
| **F, 83** | Fallen at home, immobilized. Compartment syndrome treated with fasciotomy. Sepsis caused by Staphylococcus aureus. AKI. Died after 12 days. | 1203 |
| **M, 83** | Immobilized. Pneumoniae. Unresponsive at admission. AKI. Died after two days. | 4624 |

**Table 7.** Logistic regression, predicting likelihood of developing acute kidney injury (AKI).

| | B | S.E. | Wald | df | p | Odds ratio | 95 % C.I. for Odds ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| **Maximum CK** | .000 | .000 | .001 | 1 | .974 | 1.000 | 1.000 | 1.000 |
| **Maximum myoglobin** | .000 | .000 | 11.179 | 1 | .001 | 1.000 | 1.000 | 1.000 |
| **Constant** | -0.480 | .197 | 5.952 | 1 | 0.015 | 0.619 | | |

**Figure 1a.** Correlation between creatinine and CK among a cohort of patients treated for rhabdomyolysis (n=341).

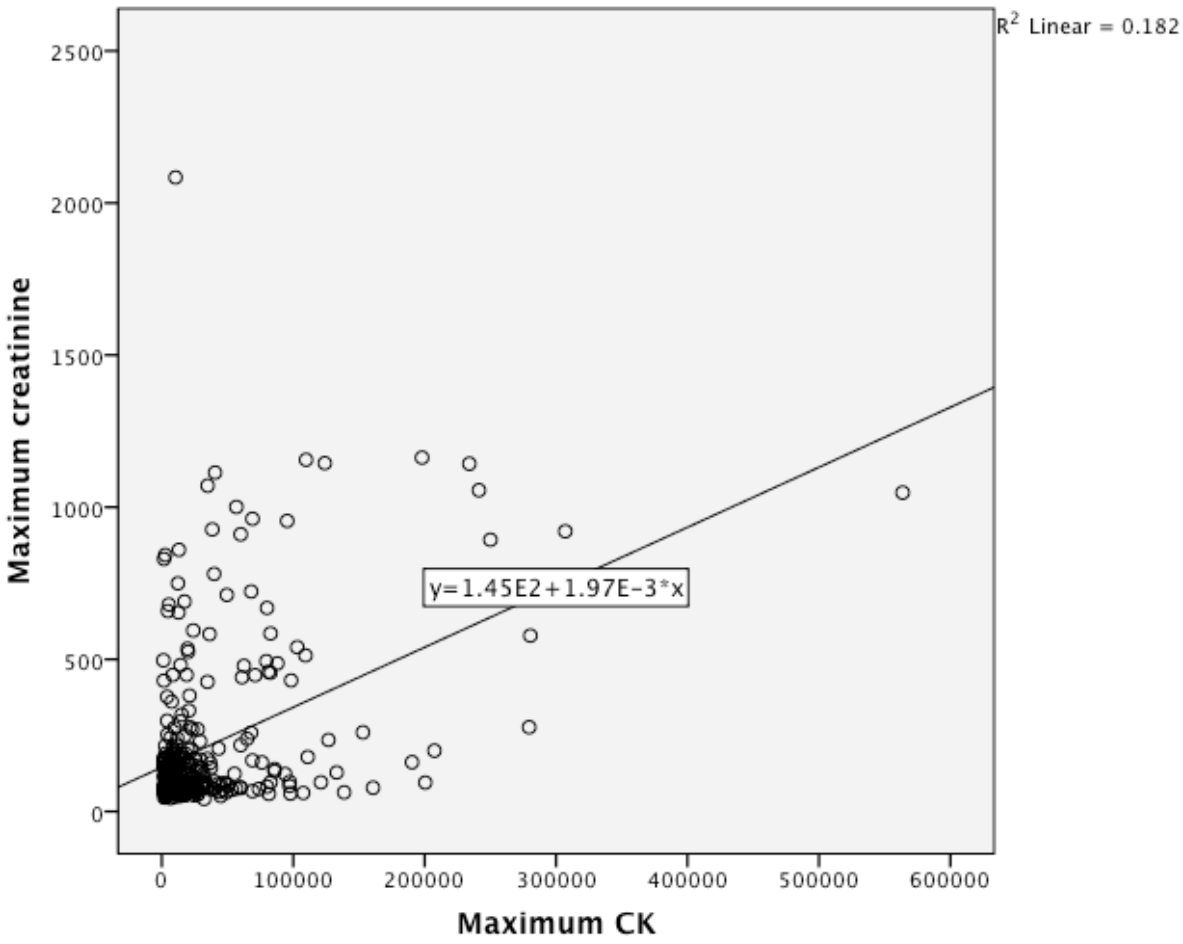

**Figure 1b.** Correlation between creatinine and myoglobin among a cohort of patients treated for rhabdomyolysis (n=341).