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# **Critical illness myopathy is frequent – accompanying neuropathy protracts ICU discharge**

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Running head: CIM frequent - CIP protracts discharge

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## **ABSTRACT**

*Objectives:* Neuromuscular dysfunction in critically ill patients is attributed to either critical illness myopathy (CIM) or critical illness polyneuropathy (CIP) or a combination of both. But it is unknown whether differential diagnosis has an impact on prognosis. This study investigates whether there is an association between the early differentiation of CIM versus CIP and clinical prognosis.

*Methods:* We included mechanically ventilated patients who featured a Simplified Acute Physiology Score II (SAPS-II)  $\geq 20$  on three consecutive days within the first week after ICU admission. 53 critically ill patients were enrolled and examined by conventional nerve conduction studies and direct muscle stimulation (184 examinations in total). The first examination was conducted within the first week after admission to the intensive care unit (ICU).

*Results:* In this cohort of critically ill patients, CIM was more frequent (68%) than CIP (38%). Electrophysiological signs of CIM preceded electrophysiological signs of CIP (median at day 7 in CIM patients vs. day 10 in CIP patients,  $p < 0.001$ ). Most patients with CIP featured concomitant CIM. At discharge from ICU, 25% of patients with isolated CIM showed electrophysiological signs of recovery and significantly lower degrees of weakness. Recovery could not be observed in patients with combined CIM/CIP even though ICU length of stay was significantly longer (mean 35 days in CIM/CIP vs. mean 19 days in CIM,  $p < 0.001$ ).

*Conclusion:* Prognoses of patients differ depending on electrophysiological findings during early critical illness: Early electrophysiological differentiation of ICU acquired neuromuscular disorder enhances the evaluation of clinical prognosis during critical illness.

**Keywords:** critical illness myopathy, critical illness polyneuropathy, direct muscle stimulation, intensive care unit

**Abbreviations:** CIM = Critical Illness Myopathy; CIP = Critical Illness Polyneuropathy; dmCMAP = Compound Muscle Action Potential after direct muscle stimulation; ICU = Intensive Care Unit; MFCV = Muscle Fibre Conduction Velocity; MUAP = Motor Unit Action Potential; neCMAP = Compound Muscle Action Potential after nerve stimulation; SAPS-II = Simplified Acute Physiology Score; SNAP = Sensory Nerve Action Potential; SOFA = Sequential Organ Failure Assessment score.

## 1 **Introduction**

2

3 Since the early description of critical illness myopathy (CIM)[1] and critical illness  
4 polyneuropathy (CIP)[2,3], the primary cause of these Intensive Care Unit (ICU) acquired  
5 weaknesses remains unresolved.[4] ICU acquired weakness complicates recovery in critically  
6 ill patients and prolongs duration of mechanical ventilation and length of stay in ICU.[5,6]  
7 Some authors advise against differentiation of CIM and CIP, as differentiation is complicated  
8 and may not result in consequences.[7,8]

9 Electrophysiological abnormalities such as low compound muscle action potentials or  
10 pathological spontaneous activity can be detected within one week of ICU admission but do  
11 not allow for distinguishing CIM and CIP.[9,10] In sedated patients without voluntary muscle  
12 contraction electrophysiological differentiation between CIM and CIP is difficult. CIM  
13 diagnosis relies on direct demonstration of muscle membrane dysfunction.[11,12] Authors  
14 using this technique of direct muscle stimulation found myopathy to be more frequent in  
15 critically ill patients.[7,11-15] CIP with associated sensory nerve involvement is assessed by  
16 a reduction of sensory nerve amplitudes, whereas assessment of motor CIP remains difficult.  
17 Rich and colleagues introduced a ratio that divides nerve evoked compound muscle action  
18 potentials (neCMAP) by direct muscle evoked compound muscle action potentials  
19 (dmCMAP) in order to differentiate between myopathy (this ratio is expected to be near 1)  
20 and motor CIP axonopathy (this ratio is expected to be small and near zero).[16]

21 In this longitudinal study of 53 critically ill patients, conventional nerve conduction studies  
22 and direct muscle stimulation were combined to determine whether there is an association  
23 between the early differentiation of CIM versus CIP and clinical prognosis.

1 **Methods**

2

3 The study was approved by our local ethics committee. Written informed consent of legal  
4 proxies was obtained according to the Declaration of Helsinki.

5 We performed this observational study in a 14-bed surgical ICU over a period of 18 months.

6 Patients who required mechanical ventilation and featured a Simplified Acute Physiology  
7 Score II  $\geq$  20 (SAPS-II)[17] on three consecutive days within the first 7 days after ICU  
8 admission were eligible for inclusion. Pre-existing neuromuscular disorders, severe head  
9 trauma or bleeding diathesis were previously defined as exclusion criteria. All patients were  
10 treated according to our standard operating procedures of intensive care medicine, adopting  
11 evidence based bundles for severe sepsis.[18,19] Severity of illness was monitored daily by  
12 repeated ratings of SAPS-II and Sequential Organ Failure Assessment score (SOFA).[20]

13

14 Every three days after admission to the ICU electrophysiological bedside studies were  
15 recorded by portable 2-Channel Keypoint Medtronic equipment (Skovlunde, Denmark). Once  
16 either CIM or CIP was detected or once patients showed adequate awareness, diagnostic  
17 testing was repeated once a week. Given that patients featured sufficient awareness at ICU  
18 discharge (Ramsay score  $\leq$  2)[21], muscle strength of upper and lower limbs was evaluated  
19 and graded according to the Medical Research Council score.[22] Whenever possible, we  
20 examined two proximal/distal muscles in each extremity and divided the total by the number  
21 of muscles examined.

22 Motor nerve conduction velocity and compound muscle action potential amplitude after nerve  
23 stimulation (neCMAP) were unilaterally performed in median, peroneal as well as in tibial  
24 nerves and recorded from abductor pollicis brevis, extensor digitorum brevis and abductor  
25 hallucis muscles. Sensory nerve conduction studies were unilaterally conducted in sural and

1 median nerves. Surface electrodes were used for stimulation and recording. In case of missing  
2 recordings or in presence of oedema, subdermal electrodes were used in all patients. Nerve  
3 conduction measurements were compared to normal values from age-matched individuals that  
4 were provided by the neurophysiological laboratory of the Charité.

5 During sedation, electromyography was performed in deltoid, biceps brachii, extensor  
6 digitorum longus, abductor pollicis brevis, rectus femoris, and tibialis anterior muscles using  
7 concentric needle electrodes to assess pathological spontaneous activity. As soon as patients  
8 showed sufficient awareness and voluntary muscle contraction was possible, quantitative  
9 electromyography was applied whenever possible in extensor digitorum longus and tibialis  
10 anterior muscles. A total of 20 different motor unit action potentials (MUAP) was sampled by  
11 random insertion of a concentric needle electrode into four different regions of an examined  
12 muscle, each recorded at 10ms, 50 $\mu$ V and filter settings of 500 Hz and 10 kHz.[23,24] Mean  
13 duration of collected non-polyphasic MUAPs was compared to normal values from healthy  
14 age-matched volunteers.[23,25]

15  
16 Assessment of compound muscle action potential amplitudes following direct muscle  
17 stimulation (dmCMAP) was performed by longitudinal placement of either conventional  
18 stimulating surface electrodes or by subdermal electrodes along muscle fibres just proximal of  
19 the distal tendon insertion in case of oedema. Muscles were stimulated by gradually  
20 increasing strength (from 10 to 100mA) at 1Hz and a pulse duration of 0.1ms. For recordings,  
21 disposable concentric needle electrodes (length 25mm or 37mm; diameter 0,46mm) and/or  
22 disposable gel surface electrodes were used and placed 15–50 mm proximal of the stimulating  
23 electrode, guided by muscle twitch. Whenever no twitch was visible, the recording concentric  
24 needle electrode was pointed at four different directions in order not to miss small amplitudes.  
25 Muscles were assumed to be inexcitable if responses could still not be obtained. dmCMAP  
26 amplitudes were measured peak to peak. Filter settings were 500 Hz and 10 kHz. Limbs'

1 temperature was ensured to be  $>32^{\circ}\text{C}$ . The examination included tibialis anterior and abductor  
2 pollicis brevis. According to Trojaborg and colleagues, dmCMAP amplitudes recorded by  
3 concentric needle electrodes  $<3\text{mV}$  were considered to be pathologic and consistent with  
4 myopathy.[11]

5 Electrophysiological measurements of tibialis anterior and abductor pollicis brevis muscles of  
6 healthy volunteers (age 22 – 74 years) in our laboratory provided reference values for  
7 dmCMAP amplitudes using surface electrodes (n=17) or concentric needle electrodes (n=8).  
8 To assess motor CIP we calculated neCMAP/dmCMAP ratios (recorded in tibialis anterior  
9 muscle with peroneal nerve stimulation at the knee AND in abductor pollicis brevis muscle  
10 with median nerve stimulation at the wrist) as introduced by Rich and colleagues: ratios  $<0.5$   
11 indicate motor neuropathy; ratios  $>0.5$  in combination with reduced dmCMAP amplitudes  
12 indicate myopathy, while ratios  $>0.5$  in presence of normal dmCMAP amplitudes display  
13 normal findings.[13]

14 To determine muscle-fibre conduction velocity (MFCV), latencies of muscle-fibre action  
15 potentials were determined and calculated for the measured distance between electrodes.

16 Perpendicular position of recording needle electrodes was ensured. Responses earlier than 8  
17 ms were likely to be conducted via intramuscular nerve twigs and not included.[11,12,14]

18 Diagnostic criteria for electrophysiological examination were as follows:

19 ICU control: patients presenting no pathology;

20 ICU unspecific: patients presenting unspecific pathology (pathological spontaneous activity  
21 and reduced neCMAP) not verifying myopathy or neuropathy;

22 CIM patients: patients presenting reduced dmCMAP in at least one muscle examined in  
23 addition to unspecific findings and normal sensory/motor nerve conduction velocity (isolated  
24 CIM);

25 CIP patients: patients presenting reduced SNAP and/or ne/dmCMAP ratio  $<0.5$  in addition to  
26 unspecific findings (isolated CIP),



1 CIM/CIP patients: patients presenting characteristics of combined CIM and CIP - reduced  
2 dmCMAP AND reduced SNAP and/or ne/dmCMAP ratio <0.5.

3 Patients were classified according to their most severe electrophysiological findings during  
4 their ICU stay. To compare electrophysiological data between patient groups, findings of the  
5 first examination presenting the most severe electrophysiological classification were chosen  
6 for each patient.

7

8 Results are expressed as arithmetic mean  $\pm$  standard deviation (SD) for electrophysiological  
9 data, median and (25/75) percentiles (if number of patients <4 only median) for categorical or  
10 non-normally distributed data, or frequencies [%] for qualitative data, respectively. Statistical  
11 tests were conducted with non-parametric tests by Mann-Whitney-U test for two independent  
12 samples, Kruskal-Wallis test for three or more independent samples, and Fisher's exact test  
13 for qualitative data. In case of small samples, greater differences in sample sizes, large but  
14 unbalanced groups, data sets containing ties, or sparse data, tests were carried out in an exact  
15 version. Diagnostic test performance was evaluated by receiver operating characteristics  
16 (ROC) analysis using MUAP duration in tibialis anterior muscle <11.1 ms as  
17 electrophysiological gold standard for diagnosing myopathy in patients capable of voluntary  
18 muscle contraction or, alternatively, using amplitudes of dmCMAP in tibialis anterior muscles  
19 of sedated patients not being capable of voluntary muscle contraction.

20 Kaplan-Meier curves were estimated to show the cumulative incidence of different  
21 electrophysiological disorders developing over time and to estimate probabilities for ICU  
22 discharge after first day of awareness in CIM and CIM/CIP patients. Differences between  
23 groups considering cumulative incidences were tested by univariate Log-Rank test.

24 In univariate Cox' proportional hazard regressions we tested the impact of CIM respectively  
25 CIM/CIP as well as illness severity on the duration between first day of adequate awareness  
26 and ICU discharge (as dependent variable). In Cox' regressions with time dependent

1 covariates, dmCMAP and SNAP amplitudes were included as indicators of myopathy  
2 respectively neuropathy while repeated recordings of SAPS-II and SOFA score during  
3 adequate awareness were included as indicators of illness severity. These variables were also  
4 analysed by stepwise (backward) procedure of multivariate Cox' regression accounting for  
5 time dependent covariates. Hazard ratios (HR) with 95%-confidence intervals (95%-CI (HR))  
6 and corresponding p-values were calculated for each risk factor.  $p < 0.05$  (two-sided) was  
7 considered as statistically significant. Statistical analysis was performed using SPSS, Version  
8 14, Copyright© SPSS, Inc., Chicago, Illinois 60606, USA, and SAS, Version 9.1, Copyright©  
9 SAS Institute, Inc., Cary, NC, USA.

1 **Results**

2

3 212 patients required mechanical ventilation and featured SAPS II  $\geq$  20 on three consecutive  
4 days within the first 7 days after ICU admission and were therefore eligible for inclusion.

5 Patients with pre-existing neuromuscular disorder (n=24), severe head trauma (n=14) or  
6 bleeding diathesis (n=33) (thrombocytopenia  $<$ 20.000/ $\mu$ l) were excluded. 16 patients could  
7 not be included due to logistical reasons. Written informed consent by legal proxy could not  
8 be obtained in 72 patients. Finally, 53 patients were included and a total of 184  
9 electrophysiological examinations were conducted. One or two examinations were conducted  
10 in nine patients each, three exams in 12 patients and four or more examinations in 23 patients.

11

12 Patient classification is shown in Figure 1. Only one patient with pre-existing Wilson's  
13 disease and two previous liver transplantations showed reduced SNAP amplitudes without  
14 evidence of motor CIP or CIM at both exams. However, pre-existing sensory polyneuropathy  
15 could not be ruled out.[26] To prevent confusion, all three patients classified as ICU  
16 unspecific as well as the only patient with isolated sensory nerve involvement were not  
17 considered in tables and figures.

18

19 Patients' characteristics are shown in Table 1.

20

21

1 **Table 1 Clinical characteristics of ICU-control, CIM- and CIM/CIP-patients**  
 2

	ICU –control (n=13)	CIM (n=16)	CIM/CIP (n=20)	p-value <sup>a</sup>	p-value <sup>b</sup>
age (years)	34 (23/51)	59 (37/67)	51 (41/58)	0.063	0.301
gender (m / f)	10/3	8/8	17/3	0.061	0.034
BMI kg/m <sup>2</sup> on admission	24.7 (21.6/26.3)	25 (22/28.5)	26 (21.9/31.2)	0.445	0.404
Sepsis on admission (%)	0%	44%	55%	0.002	0.738
Diagnosis on admission					
Multiple trauma	76.9% (n=10)	37.5% (n=6)	50% (n=10)	0.017	0.047
Cancer surgery	7.7% (n=1)	37.5% (n=6)	5% (n=1)		
ARDS / sepsis	7.7% (n=1)	25% (n=4)	45% (n=9)		
others	7.7% (n=1)	-	-		
SAPS-II on admission	26 (22/40)	39 (31/48)	41 (33/50)	0.227	0.539
SAPS-II peak (first 10 days)	36 (24/44)	40 (31/52)	54 (40/65)	0.048	0.243
SOFA on admission	8 (6/9)	9.5 (7/12)	11 (8/14)	0.006	0.149
SOFA peak (first 10 days)	8 (7/9)	10 (8/14)	12 (10/14)	0.002	0.523
Acute renal failure on admission	0%	18.8%	25%	0.157	0.709
survival (%)	100%	62.5%	80%	0.045	0.285
ICU length of stay (days)	8 (7/15)	19 (14./33)	35 (23/47)	<0.001	0.004

3  
 4  
 5 p-value<sup>a</sup> compares all three groups (Kruskal-Wallis-test / Fisher's exact test), whereas p-  
 6 value<sup>b</sup> (Mann-Whitney-U test / Fisher's exact test) compares data between CIM- and  
 7 CIM/CIP-patients. Values are shown as median and (25/75 percentiles) or as absolute  
 8 numbers. BMI = Body Mass Index, ARDS = Acute Respiratory Distress Syndrome, SAPS-II  
 9 = Simplified Acute Physiology Score, SOFA = Sepsis related Organ Failure Assessment, ICU  
 10 length of stay = Intensive Care Unit length of stay.

11

1 Amplitudes of nerve conduction studies are shown in Table 2. Predominant involvement of  
 2 the lower limbs was observed in all patients. Parameters such as motor/sensory nerve  
 3 conduction velocity, distal motor latency or F-Wave did not deviate from normal values in  
 4 any of the examined patients. Pathological spontaneous activity such as fibrillation potentials  
 5 or positive sharp waves were mostly of moderate activity and could be observed in different  
 6 muscles from patients classified as “ICU unspecific”, “CIM” and “CIM/CIP”. Tibialis  
 7 anterior and extensor digitorum longus muscles were most frequently affected.

8

9 **Table 2 Motor and sensory amplitudes for ICU control, CIM - and CIM/CIP patients.**

10

	Nerve	ICU – control (n=13)	CIM (n=16)	CIM/CIP (n=20)	p-value <sup>a</sup>	p-value <sup>b</sup>
neCMAP (mV)	Median	10.1 ± 4.3 (n=11)	6 ± 4.5 (n=11)	4.5 ± 2.9 (n=15)	0.003	0.51
	Peroneal	5.3 ± 3.7 (n=13)	2.3 ± 3.4 (n=15)	1 ± 1.2 (n=19)	0.003	0.32
	Tibial	11.8 ± 6.1 (n=13)	3.2 ± 4.1 (n=15)	3.7 ± 4.2 (n=13)	0.013	0.16
SNAP (µV)	Median	22.1 ± 7.9 (n=11)	17.3 ± 6.7 (n=11)	15.4 ± 7.6 (n=17)	0.058	0.4
	Sural	6.5 ± 3.4 (n=12)	12.8 ± 21.8 (n=15)	1.5 ± 2 (n=18)	<0.001	<0.001

11

12

13 p-value<sup>a</sup> compares all three groups (Kruskal-Wallis-test), whereas p-value<sup>b</sup> (Mann-Whitney-

14 U test) compares data between CIM- and CIM/CIP-patients. Values are given as mean ± SD.

15 neCMAP = nerve evoked Compound Muscle Action Potential amplitude, SNAP = Sensory

16 Nerve Action Potential amplitude.

17

18

19

1 Muscle specific electrophysiological data are shown in Table 3. In quantitative  
2 electromyography we observed an increased incidence of polyphasic potentials and the  
3 recruitment pattern at maximum effort was fully or only mildly reduced despite severe  
4 weakness in patients classified as “CIM / CIP” respectively “CIM” indicating a myopathy.  
5 We did not find signs of denervation such as a reduced recruitment pattern or elevated MUAP  
6 amplitudes.

7 In healthy subjects (age 22 – 74 years) dmCMAP amplitudes were not below 0.6mV when  
8 recorded by surface electrodes and not below 3mV when recorded by concentric needle  
9 electrodes. For surface electrodes 95% CI were between 0.9mV and 6mV for tibialis anterior  
10 muscle and between 0.6mV and 20mV for abductor pollicis brevis muscle. Considering  
11 concentric needle electrodes, the according 95% CI were between 4mV and 19mV and  
12 between 6.8mV and 13mV, respectively.

13 MFCV was positively correlated with dmCMAP amplitude, reduced amplitudes indicating  
14 slower MFCV (Rho = 0.55 and R Quadrate = 0.401).

15 We did not observe isolated motor CIP in any patient, as ne/dmCMAP ratios were  
16 consistently >0.5, which indicates either myopathy in presence of reduced dmCMAP  
17 amplitudes (CIM- and CIM/CIP patients) OR normal findings in presence of normal  
18 dmCMAP amplitudes (healthy subjects and ICU-controls). ROC analysis verified dmCMAP  
19 in tibialis anterior muscle during sedation as predictor of myopathy as later diagnosed by  
20 MUAP duration in the same muscle once voluntary contraction was applicable. The best  
21 relationship of sensitivity (70%) to specificity (83.3%) was observed at the cut-off value of  
22 3.2mV for dmCMAP, which is compatible to standard values from Trojaborg and  
23 colleagues.[11]

24

25

26

1 **Table 3 Muscle specific data for healthy volunteers, ICU control-, CIM- and CIM/CIP**  
 2 **patients**

3

	muscle	healthy volunteers (n=17)	ICU controls (n=13)	CIM (n=16)	CIM/CIP (n=20)	p-value <sup>a</sup>	p-value <sup>b</sup>
dm CMAP (mV) (concentric needle electrode) lower limit =3mV	Tib ant	8 ± 2.1 (n=8)	5.6 ± 1.8 (n=12)	2.2 ± 2.3 (n=15)	1.6 ± 1.9 (n=19)	<0.001	0.008
	Abd poll brev	9.3 ± 2.3 (n=6)	4.3 (n=2)	4.2 (n=2)	2.6 ± 5 (n=10)	0.136	0.006
dm CMAP (mV) (surface electrode) lower limit =0.6mV	Tib ant	2.8 ± 0.4 (n=17)	1.6 ± 0.5 (n=9)	0.3 ± 0.1 (n=9)	0.1 ± 0.1 (n=8)	0.010	0.139
	Abd poll brev	7.1 ± 5.3 (n=12)	4.5 ± 4.1 (n=5)	1.3 ± 1.7 (n=6)	0.7 ± 1.6 (n=6)	0.044	0.134
MFCV (m/s)	Tib ant	-	5.9 ± 1.6 (n=3)	5.2 ± 1.1 (n=8)	4.6 ± 1.1 (n=9)	0.454	0.335
ne/dmCMAP ratio	Tib ant	1.79 ± 1.02 (n=7)	2.2 ± 0.7 (n=9)	13.8 ± 14.6 (n=4)	4.9 ± 3.9 (n=9)	0.018	0.276
MUAP duration (ms)	Tib ant	-	11.2 ± 0.6 (n=8)	9.0 ± 2.6 (n=7)	6.9 ± 1.8 (n=10)	0.001	0.477
	Ext dig com	-	10 ± 1 (n=8)	6.3 ± 3.1 (n=9)	5.6 ± 1.1 (n=12)	0.001	0.246

4  
 5  
 6 p-value<sup>a</sup> compares ICU-controls, CIM- and CIM/CIP-patients (Kruskal-Wallis-test), whereas  
 7 p-value<sup>b</sup> (Mann-Whitney-U test) compares data between CIM- and CIM/CIP-patients. Values  
 8 are given as mean ± SD. dmCMAP = direct muscle stimulated Compound Muscle Action  
 9 Potential amplitude, MFCV = Muscle Fibre Conduction Velocity, ne/dmCMAP ratio = nerve  
 10 evoked compound action potential amplitude divided by direct muscle stimulated compound  
 11 action potential amplitude, MUAP = Motor Unit Action Potential, Tib ant = tibialis anterior  
 12 muscle, Abd poll brev = abductor pollicis brevis muscle, Ext dig com = extensor digitorum  
 13 communis muscle.

14  
 15  
 16

1 Onset of electrophysiological pathology is shown in Figure 2. Six patients could not be  
2 included in analysis due to treatment in external hospitals prior to ICU admission. Abnormal  
3 dmCMAP amplitudes occurred significantly earlier than abnormal SNAP ( $p < 0.001$ ),  
4 indicating that CIM occurs prior to CIP with associated sensory nerve involvement during  
5 early critical illness. CIM patients showed reduced dmCMAP amplitudes median at day 7  
6 (5/11) while CIM/CIP patients showed reduced SNAP amplitudes median at day 10 (4/13).  
7 Confounders prolonging ICU length of stay showed that classification as CIM or CIM/CIP  
8 independently influenced ICU length of stay whereas illness severity was comparable  
9 between both groups ( $p=0.005$ ) (Table 4).  
10 Once sedation was ended, patients classified as CIM/CIP stayed significantly longer than  
11 patients classified as CIM ( $p = 0.05$ ) (Figure 3).

12

13

14



1 **Table 4 Confounders prolonging ICU length of stay between end of sedation and ICU**  
 2 **discharge**

<b>Univariate Cox' regression with time dependent</b>	<b>Hazard Ratio[HR]</b>	<b>95%-CI[HR]</b>	<b>p</b>
<b>covariates</b>			
CIM and CIM/CIP	0.33	0.16 – 0.66	0.001
SOFA	1.05	0.95 – 1.17	0.34
SAPS-II	0.99	0.97 – 1.03	0.85
<b>Multivariate Cox' regression with time dependent covariates</b>			
<b>(after backward selection)</b>			
CIM and CIM/CIP	0.34	0.16 – 0.72	0.005
SOFA	1.05	0.89 – 1.25	0.5
SAPS-II	0.99	0.95 – 1.04	0.86

3  
4

5 Univariate and multivariate Cox' proportional hazard regression accounting for time  
 6 dependent covariates as potential confounders prolonging ICU length of stay between end of  
 7 sedation and ICU discharge (dependent variable) is shown. Analyses included dmCMAP and  
 8 SNAP amplitudes as indicators of CIM and/or CIP, respectively as well as repeated SAPS-II  
 9 and SOFA score ratings during awareness as indicators of critical illness severity. Hazard  
 10 ratios (HR) with 95%-confidence intervals (95%-CI[HR]) and p-values for each variable.

11 SAPS-II = Simplified Acute Physiology Score, SOFA = Sepsis related Organ Failure  
 12 Assessment, ICU = Intensive Care Unit, dmCMAP = direct muscle stimulated Compound  
 13 Muscle Action Potential amplitude, SNAP = Sensory Nerve Action Potential amplitude.

14

15 At discharge from ICU, some patients classified as CIM featured amplitude recovery of  
 16 dmCMAP in tibialis anterior muscles (Figure 4a) and neCMAP in tibialis and peroneal  
 17 nerves, while patients classified as CIM/CIP consistently showed reduced amplitudes of  
 18 dmCMAP and neCMAP (Figure 4b).

19 At ICU discharge, muscle strength according to the MRC-score was significantly lower in  
 20 patients classified as CIM/CIP (n=14; examination was precluded in 4 patients due to death  
 21 and in 2 patients due to logistical reasons; mean MRC-score in upper limbs 3.5; mean MRC-

1 score in lower limbs 3.25) than in patients classified as CIM (n=8; examination was precluded  
2 in 6 patients due to death and in 2 patients due to logistical reasons; mean MRC-score in  
3 upper limbs 4.5, p=0.002; mean MRC-score in lower limbs 4.0, p=0.004).  
4

## 1 **Discussion**

2

3 Direct muscle stimulation facilitates diagnosis of CIM in the early course of critical illness.

4 During analgesia and sedation, other methods of clinical assessment are not applicable.

5 Electrophysiological signs of CIM precede electrophysiological signs of CIP. Isolated CIP

6 was not observed in any patient, it occurred only in combination with myopathy. Clinical

7 courses of patients classified as CIM respectively CIM/CIP differ. Both CIM and CIM/CIP

8 independently influence ICU length of stay after the end of sedation. However, patients

9 classified as CIM/CIP feature significantly higher degrees of weakness at ICU discharge and

10 longer ICU lengths of stay than patients classified as CIM. Electrophysiological recordings

11 displayed that some patients classified as CIM showed signs of recovery at discharge from

12 ICU while all patients classified as CIM/CIP consistently featured electrophysiological

13 pathology at ICU discharge.

14

### 15 ***Technical aspects***

16 By comparing dmCMAP amplitudes with MUAP duration in quantitative electromyography -

17 the gold standard of proving myopathy [23,24] - we could show that assessment of dmCMAP

18 amplitudes represents a valuable tool to differentiate between CIM and CIP during the early

19 course of critical illness, when voluntary muscle contraction is not applicable due to sedation

20 (sensitivity 70%, specificity 83.3%).

21 The technique of direct muscle stimulation has been evaluated in healthy subjects[27,28] and

22 patients suffering from weakness and/or weaning failure caused by critical illness.[7,11-

23 13,29] Published reference data for dmCMAP depend on recording characteristics of

24 electrodes: *concentric needle electrodes* (Trojaborg et al., 2001:  $8.0 \pm 0.9\text{mV}$ , lower limit  $\geq$

25  $3\text{mV}$ , n = 18; Lefaucheur et al., 2006:  $9.61 \pm 2.36\text{mV}$ , lower limit  $\geq 4.88\text{mV}$ , n = 12 AND

26 our data:  $8.0 \pm 2.1\text{mV}$ , lower limit  $\geq 3\text{mV}$ , n = 8), *subdermal electrodes* (Trojaborg et al.,

1 2001:  $4.5 \pm 1.7\text{mV}$ , lower limit  $\geq 1\text{mV}$ ,  $n = 18$ ), or *surface electrodes* (our data:  $2.8 \pm 0.4$ ,  
2 lower limit  $\geq 0.6\text{mV}$ ,  $n = 17$  ). Assessing dmCMAP with surface electrodes may be of  
3 advantage in patients with bleeding diathesis. However, measurements with concentric needle  
4 electrodes have the advantage of also recording smaller activity from within the deeper  
5 muscle.

6  
7 MFCV values of healthy subjects (Troni et al., 1983:  $3.53 - 4.24$  m/s male and  $2.96 - 3.74$   
8 m/s female; Trojaborg et al., 2001:  $6.4 \pm 0.3$  m/s; Allen et al., 2008:  $3.0 - 5.5$  m/s) and CIM  
9 patients (Trojaborg et al., 2001:  $4.5 \pm 0.2$  m/s; Allen et al., 2008:  $2.32 \pm 1.12$  m/s, our data:  
10  $5.2 \pm 1.1$ m/s) are various. Interestingly, patients classified as ICU control showed a reduction  
11 of MFCV ( $5.9 \pm 1.6$ m/s,  $n = 3$ ) and dmCMAP amplitude ( $5.6 \pm 1.8\text{mV}$ ,  $n = 12$ ) compared to  
12 healthy volunteers (our data and Trojaborg et al., 2001), possibly indicating early impairment  
13 of muscle membrane excitability on a subclinical level that is not accompanied by distinct  
14 levels of weakness after the end of sedation.[15] This indicates, that critical illness in general  
15 causes impairment of muscle membrane excitability, however, in order to cause muscle organ  
16 failure an additional pathomechanism is essential.

17  
18 Ne/dmCMAP ratios  $<0.5$  are supposed to indicate motor axonopathy.[16] Since this ratio was  
19  $>0.5$  in all of our patients the presence of motor axonopathy is questionable. Z'Graggen and  
20 colleagues assessed the existence of membrane depolarization in motor nerves by applying  
21 nerve excitability testing[30], proving a nerve membrane affection but not finally proving the  
22 existence of a motor axonopathy.

23 It should be emphasised that SNAP abnormalities indicate sensory neuropathy and cannot  
24 serve as definite evidence towards neuropathic involvement in clinical weakness. Early  
25 reports attributed weakness in critically ill patients mostly to distal motor axonopathy on the  
26 basis of non-specific electrophysiological abnormalities and neglected the possibility of

1 primary muscle fibre disorder.[3,31] By applying the technique of direct muscle stimulation,  
2 we and others, were able to show that CIM is frequent in critically ill patients.[7,11-15]  
3 However, ne/dm CMAP ratios did not add further information to the diagnosis of myopathy  
4 than dmCMAP amplitudes.

5

## 6 ***Clinical aspects***

### 7 *Onset and incidence of neuromuscular disorder*

8 To the best of our knowledge, this is the first study reporting that CIM is verified significantly  
9 earlier than CIP. Unspecific findings such as pathological spontaneous activity or reduced  
10 neCMAP amplitudes do not differentiate CIM and CIP and were observed within the first  
11 week after ICU admission. This is in line with three earlier studies describing early onset of  
12 neuromuscular dysfunction in the ICU without differentiating between myopathy and  
13 neuropathy.[9,10,32] We presume that early pathological spontaneous activity is related to  
14 muscle membrane depolarization leading to elevated excitability.

15 Coexistence of pathological spontaneous activity and reduced dmCMAP amplitudes was  
16 surprising to us, as we expected a reverse relationship due to contrary pathology. However,  
17 this is in line with findings from a rat-model of CIM describing concomitant membrane  
18 depolarization and reduced excitability, which was attributed to voltage-gated sodium-channel  
19 dysfunction.[33,34] It was furthermore reported, that endotoxin of gram-negative bacteria  
20 causes a hyperpolarized shift in the gating of voltage-gated sodium channels in human  
21 skeletal muscle,[35] which in presence of muscle membrane depolarization in critically ill  
22 patients [36] will finally cause muscle membrane inexcitability.

23 We observed both systemic inflammation and illness severity during early critical illness to  
24 present significant risk factors for development of CIM or CIM/CIP. It nevertheless remains  
25 unresolved why some patients show more severe or combined affection of muscles and nerves  
26 than others.

1 *Recovery from neuromuscular disorder*

2 Some authors advise against adoption of electrophysiological differential diagnosis [7,8] since  
3 distinguishing between CIM and CIP would not be associated with clinical prognosis. We  
4 recently reported that CIM constitutes the primary reason for ICU acquired weakness  
5 presenting in critically ill patients suffering from sepsis, systemic inflammatory response  
6 syndrome or multiple organ failure once sedation is ended.[15] For the first time we report  
7 that ICU length of stay is markedly prolonged in patients classified as CIM/CIP compared to  
8 patients with isolated CIM and that this does not result from illness severity after sedation was  
9 ended. Expecting subsequent prolongation of recovery time, it was interesting to observe that  
10 patients classified as CIM/CIP still featured severe weakness at ICU discharge in contrast to  
11 CIM patients. This is consistent with observations by Guarneri and colleagues describing  
12 better long-term prognosis (one year after hospital discharge) in patients diagnosed with  
13 isolated CIM.[37] It should nevertheless be mentioned that patients classified as CIM/CIP  
14 showed more pronounced dmCMAP amplitude reduction and shorter MUAP duration, both  
15 characteristics of pronounced myopathy, than patients with pure CIM.

16  
17 As some CIM patients show recovery of dmCMAP amplitude reduction at ICU discharge, we  
18 presume inactivation of voltage-gated sodium channels in structural intact muscle fibres to be  
19 reversible after successful treatment/elimination of potentially involved factors, which would  
20 explain return to normal function within days.[7,11,13,38] Recovery was not observed in  
21 patients classified as CIM/CIP, which may be either due to pronounced muscle dysfunction  
22 with selective myosin-filament loss in fast twitch muscle fibres OR due to muscle denervation  
23 causing muscle membrane depolarization potentially counteracting recovery.[11,36,38,39]

24  
25 In conclusion, we were able to show that clinical prognosis differs according to  
26 electrophysiological differential diagnosis during early critical illness. CIM in combination

1 with CIP was associated with more severe weakness at ICU discharge and longer ICU length  
2 of stay than isolated CIM. During the early course of critical illness, when voluntary muscle  
3 contraction is not applicable due to sedation, we recommend conventional  
4 electrophysiological recordings in combination with direct muscle stimulation (adds another  
5 5-15 min) to maintain precise differential diagnosis. This supports better prediction of  
6 weaning difficulties which occur in both CIM and CIM/CIP patients and furthermore assists  
7 clinicians in estimating motor function recovery at ICU discharge.

8  
9

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13  
14  
15  
16

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5

6

1 **Legends for figures**

2

3 **Figure 1** Consort Diagram for electrophysiological characteristic. SAPS-II = Simplified acute  
4 physiology score, ICU = Intensive care unit, neCMAP = nerve evoked compound action  
5 potential amplitude, dmCMAP = direct muscle stimulated compound action potential  
6 amplitude, SNAP = sensory nerve action potential amplitude.

7

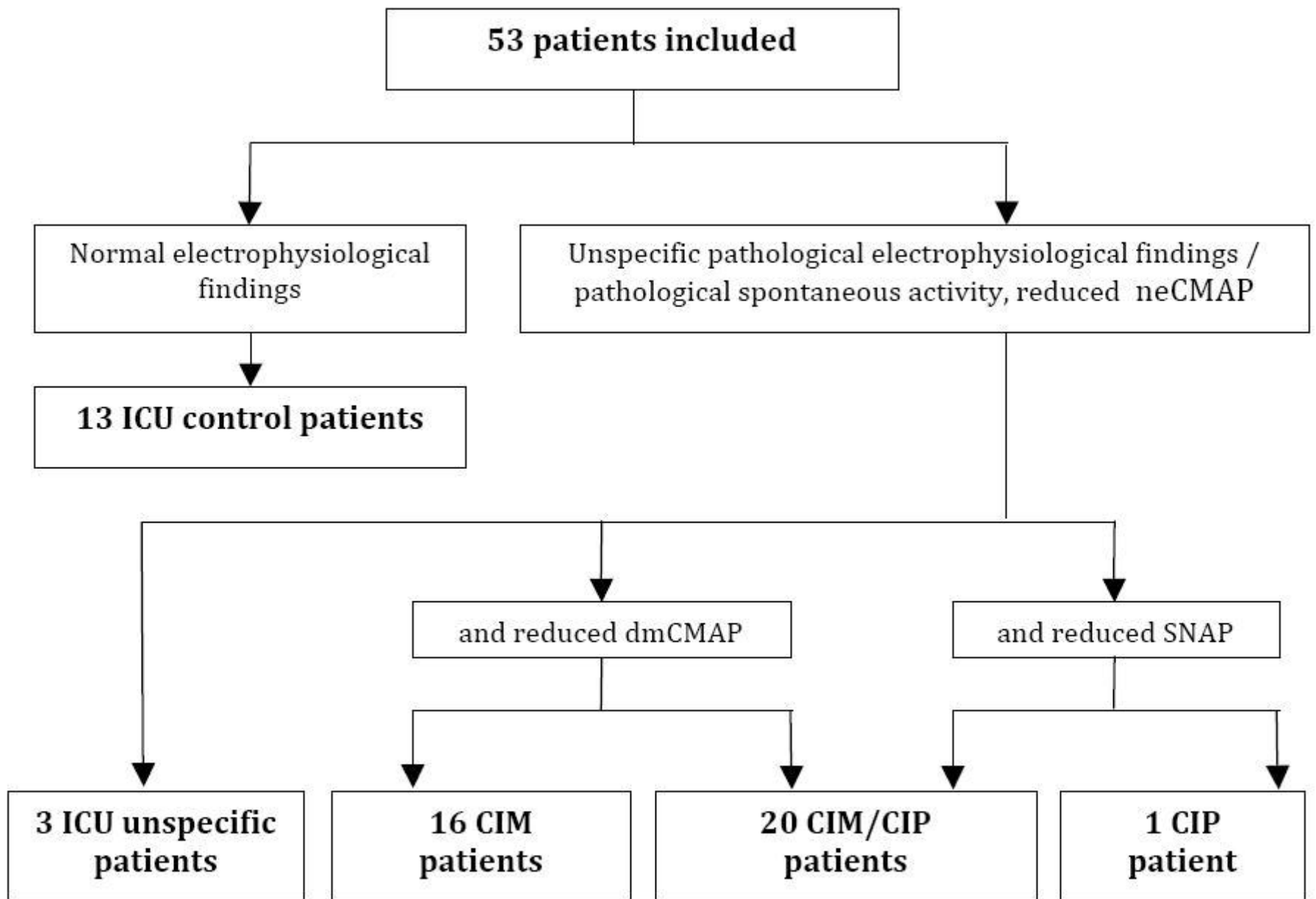
8 **Figure 2** Cumulative incidence of neuromuscular affection in days after onset of critical  
9 illness. Probability 0.5 for pathological spontaneous activity (short/long dashed line n=34) is  
10 median 5 days (4.82/ 7.18 95% CI), for reduction of neCMAP amplitudes (short/long dashed  
11 line (n=40) 6 days (3.88 / 6.12 95% CI); for reduction of dmCMAP amplitudes (solid line, n =  
12 30) 9 days (6.38 / 11.6 95% CI) and for reduction of SNAP amplitude (short dashed line,  
13 (n=17) 18 days (4.01 / 31.9 95% CI). Time differences are significant for dmCMAP vs.  
14 pathological spontaneous activity and neCMAP ( $p < 0.01$ ) and vs. SNAP ( $p < 0.001$ , Log  
15 Rank test). Crosses per line denote censored observation without showing pathological signs.  
16

17 **Figure 3** Cumulative Probability for ICU length of stay counted from the day after awakening  
18 from sedation until discharge from ICU for CIM – patients (solid line) and CIM/CIP –  
19 patients (dashed line) ( $p = 0.054$ ; Log Rank test).

20

21 **Figure 4** Time course for dmCMAP after onset till discharge of ICU stay organized in time  
22 groups (1-3 days, 4-6 days, 7-9 days, 14-18days, 19-24 days and 25-31 days) for ICU-control,  
23 CIM- and CIM/CIP-patients; for (A) dmCMAP amplitude of tibialis anterior muscle,  
24 reference mark at 3mv (normal  $\geq 3\text{mV}$ ); box plots show median and (25%/75%)  
25 percentile. ICU-control (black boxes), purely CIM- (diagonal Boxes) and CIM/CIP patients  
26 (blank Boxes). (B) Difference of neCMAP and dmCMAP amplitude at discharge from ICU

1 for ICU-control, CIM- and CIM/CIP-patients. Differences are shown for CIM/CIP patients  
2 vs. purely CIM-patients (Kruskal-Wallis test). neCMAP = nerve evoked compound action  
3 potential amplitude, dmCMAP = direct muscle stimulated compound action potential  
4 amplitude.  
5



**Figure 1**

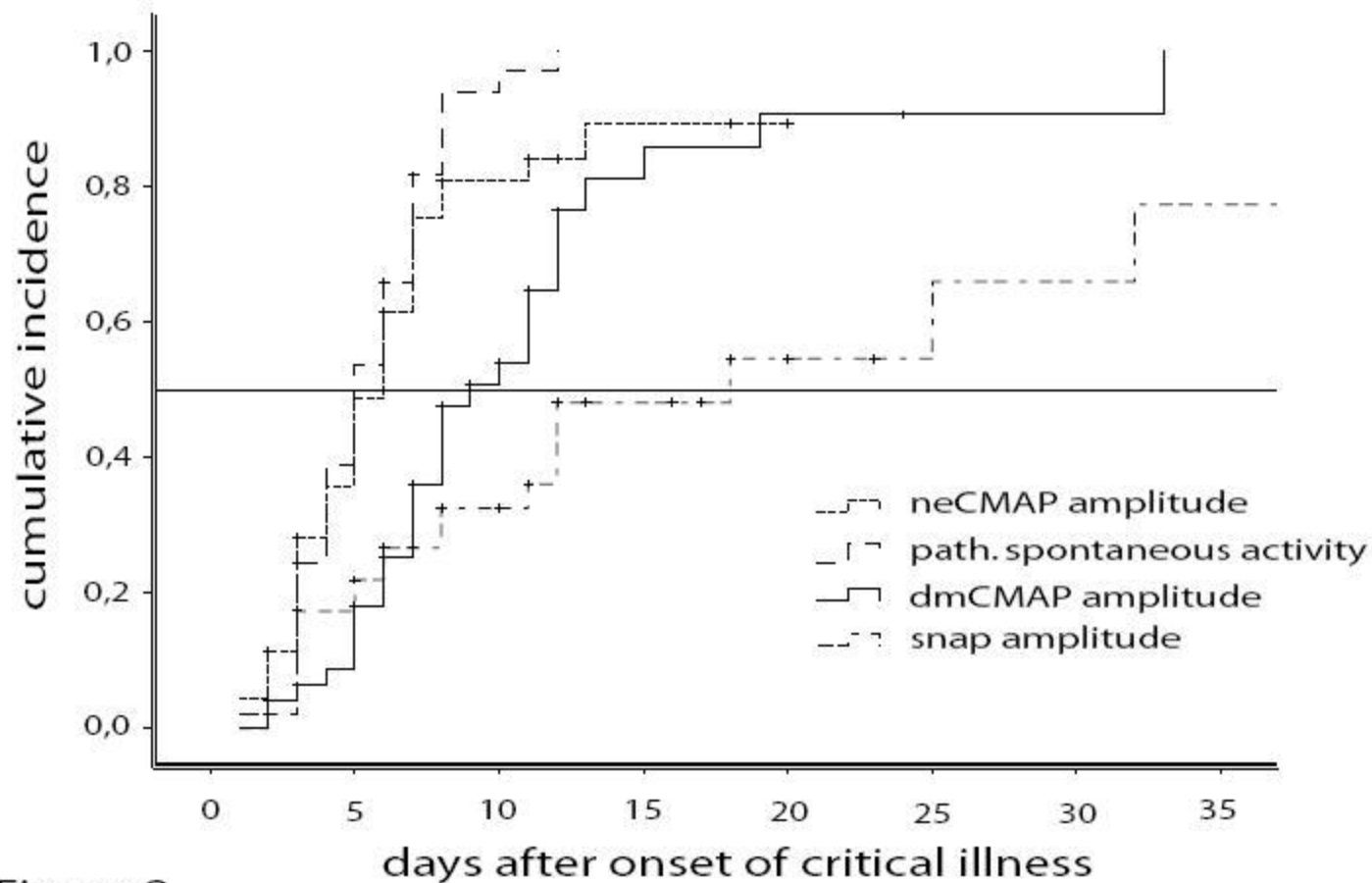


Figure 2



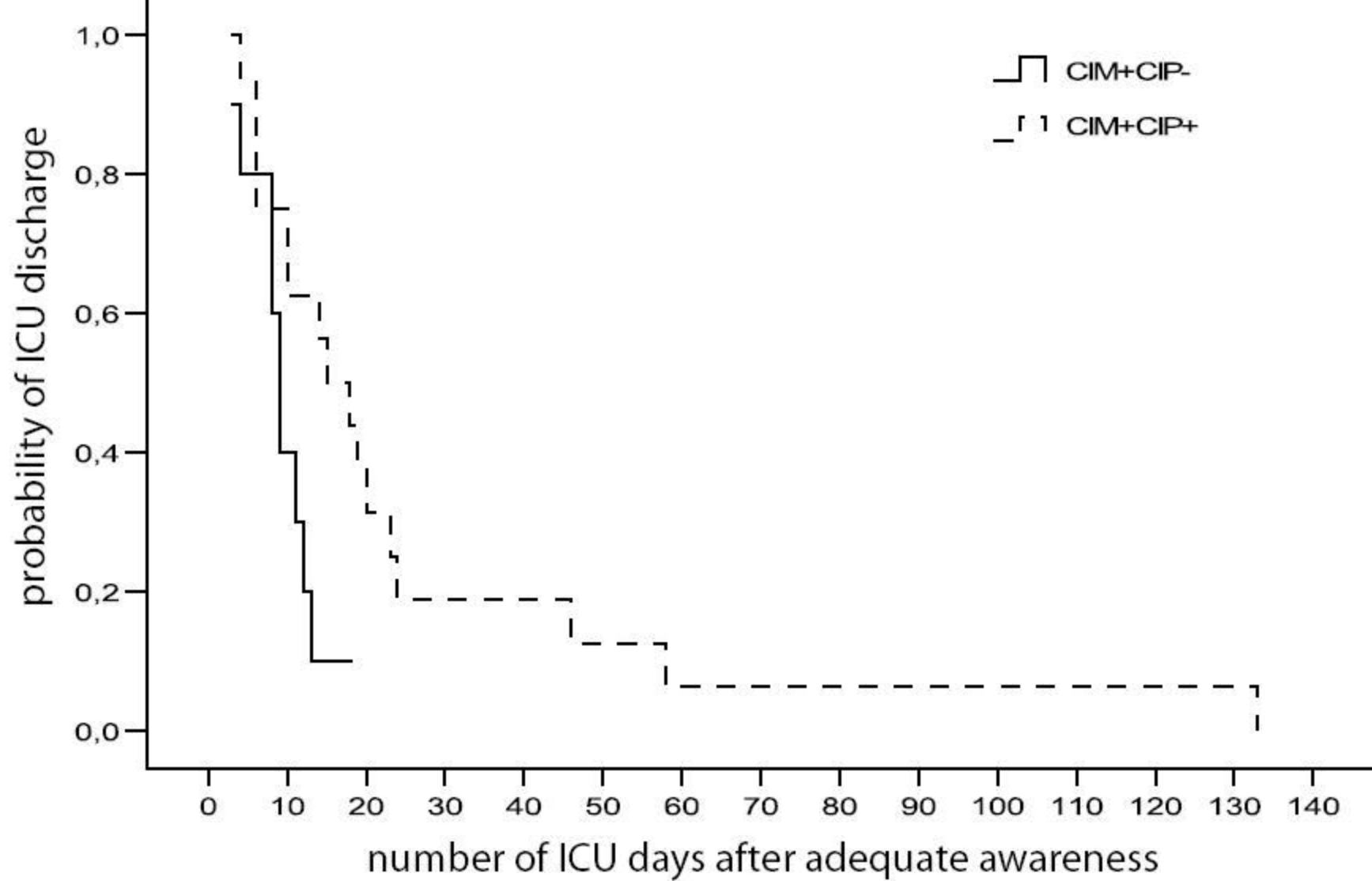


Figure 3

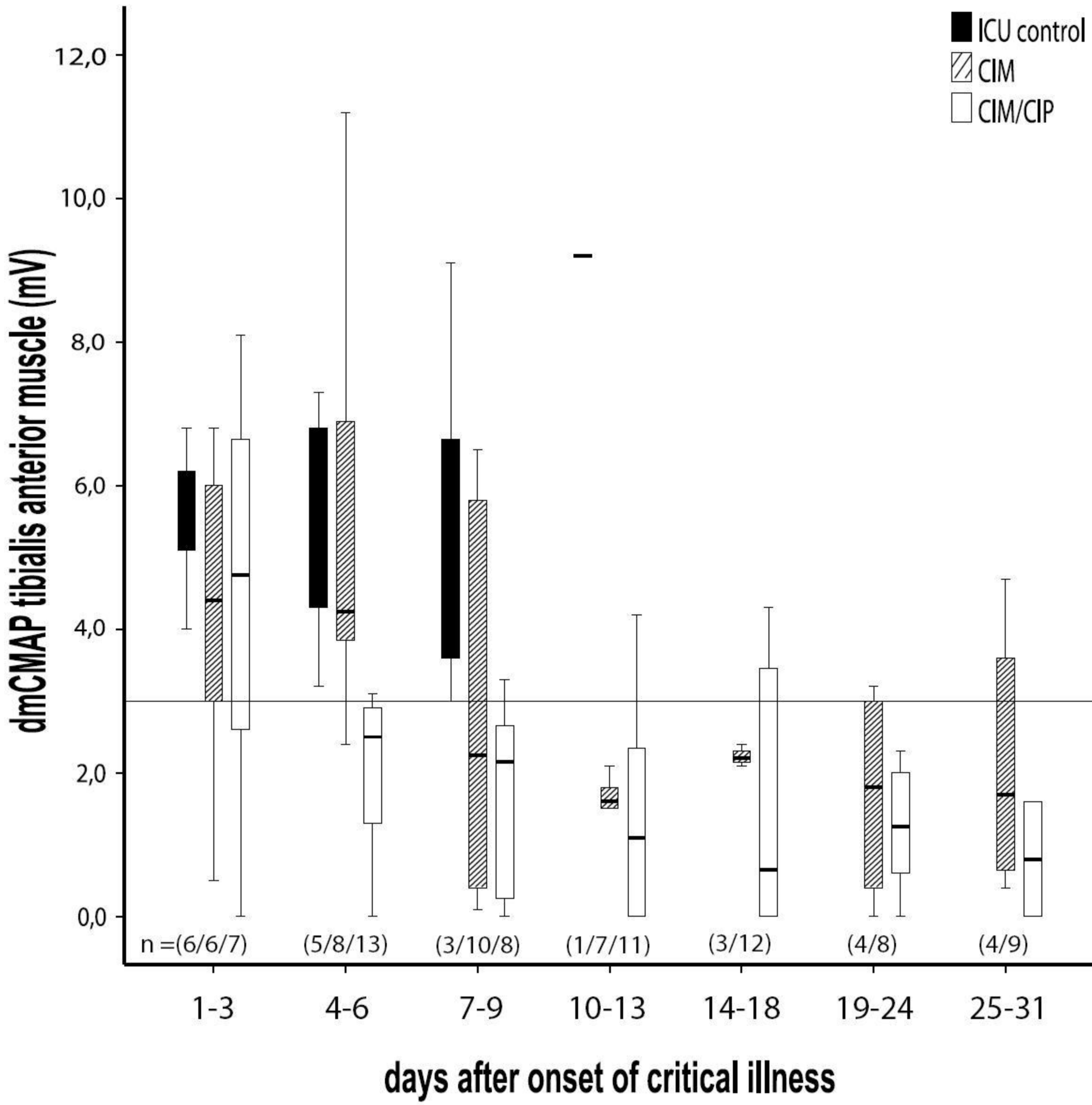


Figure 4a

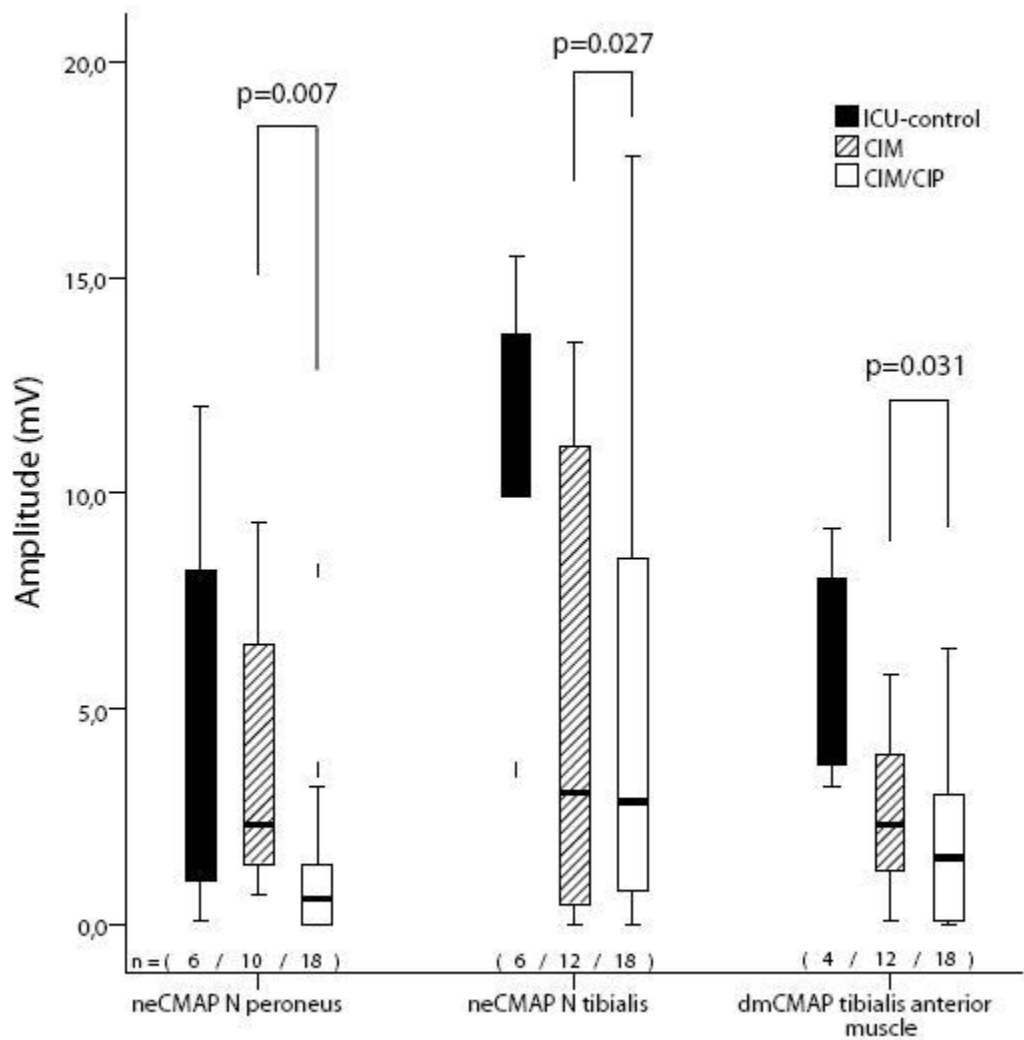


Figure 4b