Introduction

Intensive care admission causes profound physical and psychological stress to both patients and their relatives [1,2]. If the patient recovers from critical illness a new challenge starts: rehabilitation to a ‘normal’ life - if ever possible. Surviving intensive care usually carries a significant degree of morbidity, disability and emotional stress which can be long-lasting. However, survival is still regarded as the most important outcome in intensive care medicine and less attention has been given to the intensive care-related problems that patients may encounter after critical illness, the so-called patient-centred outcomes [3]. These sequelae are diverse, dynamic and are not solely related to the extent of organ damage and the initial diagnosis [3,4]. The complex nature of these sequelae resides in the heterogeneity of the premorbid health status and initial insult, the individuality of the host’s response to the insult, the extent of organ failure, the medical and nursing care received and the time spent in the intensive care unit (ICU).

More literature is emerging that evaluates the sequelae of a period of critical illness [1,5-8]. Moreover, there is growing interest in ICU follow up and post-ICU care [9].

The objective of this review is to provide an overview of observed physical and psychological sequelae, impairments and disabilities encountered by patients recovering from a critical illness and ICU.

Methods

PUBMED and EMBASE databases were searched for relevant controlled trials, cohort studies, meta-analyses and reviews using the following search strategy:

("Intensive Care Unit"[Mesh] OR "Critical Illness"[Mesh])
AND ("Follow-Up Studies"[Mesh] OR Outcome)
AND (morbidity OR impairment OR disability OR quality of life)
AND discharge.

Using search limits, only studies concerning adult humans and published in the Dutch, English or German language were included. Citations (title and abstract) were selected based on their relevance. Only articles concerning follow up of patients discharged from ICU, the physical or psychological problems experienced in relation to ICU admission or critical illness, and the aetiology of such problems were subject to further review. Only citations that were clearly not relevant were not subject to further review. All papers identified were searched for further relevant references.

Results

Search results
Searching the PUBMED and EMBASE databases identified 180 and 195 citations respectively. Only ten of these fitted inclusion criteria and were subject to further review. Cross-referencing identified an additional 47 papers. These papers mainly concerned theories on the aetiology of identified sequelae and provided new data and evidence on sequelae. Given the broad nature of this subject, less specific search strategies led to an excessive number of search results and proved irrelevant. In the identified papers several sequelae were reported which are discussed in the following sections. (Table1)
1. Physical impairments

Critical illness may cause specific problems that can be related to the underlying illness but also to treatment and stay in an ICU. Critical illness leads to numerous hormone and cytokine-mediated stress responses, including inflammatory, immune, hormonal- and metabolic changes resulting in organ failure [10,11]. The severity of disease and the degree of organ dysfunction can be measured by scoring systems such as the APACHE II and SOFA scores, and is related to short-term outcome parameters such as mortality [12,13]. Organ failure can be permanent, for example acute kidney injury leading to irreversible renal failure and chronic dialysis treatment. Of the four percent of critically-ill patients in intensive care who required renal replacement therapy, 12.5% were dialysis-dependent after one to ten years [14]. Survivors of the acute respiratory distress syndrome (ARDS) showed mild to moderate abnormalities on spirometry one year after discharge. These abnormalities correlate with pulmonary symptoms and health-related quality of life (HRQoL) [15].

However, some hypothesize that organ failure is more a functional than a structural problem and an attempt by the body to preserve cells during critical illness by putting them in a dormant state in order to contain damage [10]. This theory implies that organ dysfunction in the acute phase is not necessarily related to poor long-term outcome in those who survive critical illness. This is supported by the findings of Clermont et al. who after controlling for baseline health status, showed that the presence of acute organ dysfunction was not predictive of mortality or HRQoL 90 days after onset of community acquired pneumonia [16].

<table>
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<tr>
<th>Physical impairments</th>
<th>Persistent organ failure</th>
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<td>- Renal</td>
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<td>- Pulmonary</td>
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<td>Hair loss / alopecia</td>
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<td>Reduced appetite</td>
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<td>Weight loss</td>
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<td>Weakness</td>
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<td>Joint immobility / contractured fingers</td>
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<th>Psychological impairments</th>
<th>Sleeping disorders</th>
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<td>Depression</td>
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<td>- Post traumatic stress disorder</td>
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<td>Cognitive impairments, e.g.:</td>
<td>- Memory, concentration</td>
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<td></td>
<td>Loneliness</td>
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<td>Irritability</td>
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<th>Functional status</th>
<th>Diminished quality of life, e.g.:</th>
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<td></td>
<td>- Physical function</td>
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<td>Impairment in activities of daily life</td>
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Apart from the effects of persistent organ dysfunction, discharged ICU patients may experience a spectrum of physical problems. In a group of 83 ARDS survivors, temporary alopecia was reported in most patients, as well as entrapment neuropathies in six patients (7%), joint enlargement and immobility in four patients (5%) and contractured fingers or frozen shoulder in three patients (4%), probably due to immobilization [17]. Hair loss and dry hair were also reported by 17 of 54 patients (31%) three months after ICU in a follow-up study by Daffurn et al. [18]. Dry scaling skin has also been observed. Reduced appetite was reported by one fifth [18]. Although some of the problems mentioned above may seem relatively harmless they may certainly influence quality of life.

Weight loss is a common problem for ICU survivors and signifies the extent of catabolic response during and after critical illness [17-19]. Although protein synthesis seems to be normal or only slightly affected in patients with sepsis and multi-organ failure, degeneration of proteins is increased [20,21]. At ICU discharge, 109 survivors of ARDS had a mean loss of 18% of their baseline body weight. One year after discharge only 59 of 83 patients (71%) returned to their baseline weight [17]. A study by Kvale et al. showed that 69% of patients lost more than five kg of body weight during ICU stay. Moreover 40% (55 of 136) of patients lost 10 kg or more. Weight loss was not related to length of stay or duration of ventilation [19].

Muscle wasting, including wasting of the respiratory muscles, can be significant and can prolong weaning from mechanical ventilation [21]. In addition, mechanical ventilation causes atrophy of respiratory muscles [22].

Weakness is common and poses a major problem in the rehabilitation phase. It is reported by patients to be one of the most important reasons for functional limitations after discharge [17]. In addition to degradation of muscles, neuronal damage due to critical illness polyneuromyopathy (CIPM) causes weakness after intensive care stay. Critical illness polyneuropathy (CIP) is an acute polyneuropathy predominantly affecting motor neurons and usually presenting as flaccid tetraparesis. CIP causes neurogenic atrophy in muscles and axonal degeneration in nerves [23]. It can be regarded as an end-organ system failure and part of the multiple organ dysfunction syndrome. CIP is considered to be the most common neurological disorder among critically-ill patients and the incidence reaches 50% or more in the ICU [24].

Some patients with weakness have normal neuronal activity with evidence of myopathic changes on muscle biopsy and suffer from primary critical illness myopathy (CIM) [24].

Risk factors for the development of polyneuromyopathy (CIPM) include higher severity of illness (APACHE II) scores and sepsis [24]. Moreover, medications such as corticosteroids, muscle relaxants and aminoglycosides are risk factors [17,24]. Other risk factors reported include parenteral nutrition, autoimmune disorders, hyperosmolality, osmolality changes and catecholamine use in the treatment of shock [24]. A recent meta-analysis shows that strict glucose control can reduce the incidence of CIPM [25].

Recovery from CIPM can be complete, but rehabilitation can be prolonged. Persistent motor or sensory deficits have been reported up to five years after discharge from a prolonged ICU.
stay [26]. CIPM is known to affect functional outcome after discharge from ICU, limiting social functioning and leading to an unsatisfactory quality of life [26,27].

2. Psychological and cognitive impairments
Apart from physical impairments, mental health can continue to be affected for months after discharge. The importance of psychological sequelae has been recognized since 1983, when psychological changes commonly seen after an ICU admission were named the ‘ICU-syndrome’ [28].

The threat of impending death in the critically ill causes a psychological stress response. Critically-ill ICU patients have clear reasons for feeling anxiety - the occurrence of the illness itself and the experience of the ICU environment [11]. Feelings experienced include loss of control, fear, pain, anxiety, lack of sleep, inability to express or communicate, nightmares and loneliness [29, 30]. Technical procedures and treatment itself, e.g. weaning from a ventilator, can cause stress [31]. As sedatives are withdrawn, the weaning process is often one of the first memories patients may have [32]. With wakefulness comes awareness of the illness and of the unknown and busy ICU environment.

Delirium is another frequently-encountered problem contributing to psychological sequelae in critically ill patients. The reported prevalence of delirium varies from 20 to 80 percent [33]. Hallucinations, disorientation and anxiety are often experienced by these patients.

After discharge patients are faced with limitations. The process of recovery and acceptance of a new role in daily life can cause fear and affect mood [29]. In a study by Datfurn et al. over one-third of patients reported loneliness, irritability or depression three months after discharge [18]. Delayed physical recovery after intensive care may contribute to psychological morbidity [5].

Sleeping problems and tiredness are particularly worrying to patients discharged from ICU [18]. One-fifth of patients reported that they were sleeping worse eight months after discharge than before the stay in intensive care [19]. A recent large multi-centre study found at follow-up that concurrent disease was strongly associated with sleep disturbances after ICU, suggesting that it is not merely the ICU stay but also underlying illness that causes sleeping problems [34]. Nightmares are common after a stay in intensive care and can in fact be part of post traumatic stress disorder (PTSD).

A significant number of patients experience anxiety and depression after discharge from ICU. Scragg et al. found that 24 of 80 ICU survivors (30%) scored above the threshold for clinically significant depression on the Hospital Anxiety and Depression Scales (HADS) subscale for depression [35]. Moreover, 34 of 80 (45%), experienced clinically significant anxiety symptoms on the HADS anxiety subscale.

In addition to symptoms of anxiety and depression, patients may be confronted with intrusive recollections of their stay in intensive care as part of PTSD, which is an anxiety disorder. Symptoms of PTSD and anxiety or depression are related [31,35-37]. In order to diagnose PTSD, criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV have to be met and present for at least one month. Criteria include the occurrence of a traumatic event - often the illness or ICU stay itself. Subsequently, the patient may re-experience this event, for example in the form of intrusive recollections or dreams. There may be signs of avoidance or numbing of feelings related to the event. Moreover the patient can have increased arousal leading to sleep disturbances or difficulties in concentrating [38].

Several studies, including a meta-analysis report PTSD rates of around 15% (13-15.6) in the months after ICU discharge [35,39,40]. If the gold standard for diagnosing PTSD is used - the standardized clinical interview - prevalences range from 0-64%. Timing of follow-up may influence reported incidences as PTSD symptoms tend to decrease over time [41]. However, a retrospective study among ARDS survivors by Kapfhammer et al. finds an increased incidence of PTSD up to 8 years after discharge [31,41]. Relatives of ICU patients are also affected and even show PTSD-like symptoms [42]. In a study by Azoulay and co-workers, up to one-third of relatives questioned reported PTSD-like symptoms three months after discharge [36]. Moreover, levels of PTSD symptoms in family members relate to levels of PTSD symptoms in patients [43,44].

Patients who remember parts of their stay in ICU have either factual or delusional memories, the latter of which predisposes to experiencing psychological problems after ICU [32,45,46]. Amnesia is one of many cognitive impairments experienced after discharge from ICU. The domains of cognitive function most often reported to be impaired include memory, executive function, attention and processing speed [47]. Amnesia is common in ICU patients and a direct and desirable consequence of sedation. However, a significant number of patients do not have any memory of the ICU at all even though sedation is withdrawn before ICU discharge. Weinert et al. found that 18% of patients requiring more than 36 hours of mechanical ventilation did not remember anything from their time in the ICU and in a study by Kvale and co-workers, this was 43% at seven months post-discharge [19,32]. Amnesia is not limited to the ICU but may also cover the time before admission and the period after discharge [48]. Although cognitive impairments improve in the first year after discharge, long-term follow up of 62 patients showed that 29 of 62 (47%) had cognitive impairments lasting for years [5,49].

3. Functional problems and quality of life
Functional capacity is limited after ICU discharge. A study by Chelluri et al. measured the ability to independently perform activities of daily life (ADL) and instrumental activities of daily living (IADL). The IADL are more complex activities such as shopping and household chores. More than half (57%) of all 231 survivors required caregiver support one year after discharge. Older patients and patients who were IADL-dependent before admission were more likely to be IADL-dependent one year after discharge. Only 28% of patients were fully IADL-independent one year after discharge. The median age of this surviving group was 53 [50].

Critical illness and intensive care admission influence working status. The percentage of non-workers increased from 40.4%
before admission to 64.7% seven months after discharge from a university hospital ICU in a follow up by Kvalø et al. [19]. Clermont et al. found an association between the number of organ failures during ICU admission and working status three months after intensive care discharge among patients admitted to ICU for pneumonia, suggesting that severity of acute illness influences functional status after ICU [16].

Health-related quality of life (HRQoL) is lower in discharged intensive care patients when compared with control groups [5,6,31,51-53]. Although rapidly improving while recovering from critical illness, HRQoL remains significantly lower up to 14 months after ICU discharge [17,51,52].

Kaarlola et al. studied quality of life up to six years after discharge from ICU. Former ICU patients reported more bodily pain, worse general health and worse physical functioning than controls [53]. On the contrary, one follow up trial by Graf and co-workers among 246 medical ICU patients from a university hospital showed a return towards baseline HRQoL nine months after ICU discharge, irrespective of age [4].

Discussion
A significant number of discharged ICU patients suffer from psychological and/or physical morbidity which may cause functional limitations and influence quality of life. Awareness of these sequelae is growing, however, their exact mechanisms and causes are not fully understood.

Various pre-ICU factors such as age, co-morbidity, underlying disease and ethnicity influence outcome [54,55]. On the other hand there is evidence that experiences of stress, medication and the ICU environment influence the incidence and magnitude of ICU sequelae. The aetiology of ICU sequelae is therefore a complex interaction between patient-related factors and ICU-related factors. Moreover, these factors will differ between hospitals and ICU settings thus complicating their analysis. When conducting research on this subject, it is essential to sample data on the health status of subjects before ICU admission and to correct for these confounding factors. This is an absolute requirement for identifying any causative association between ICU-related factors and sequelae, as the morbidity after ICU might be attributed to the course of chronic disease or co-morbidity, rather than ICU stay itself. For example, in a follow up study by Jones et al., 17% of former intensive care patients already had a history of anxiety or depressive disorders before ICU admission [46]. Identifying aetiological factors or risk factors may help to find interventions aimed at modifying or eliminating these factors in order to prevent or lessen ICU sequelae.

Follow up of ICU patients is usually conducted by the general practitioner or other specialists. If physical or psychological sequelae are identified, information on their origin can be provided and if necessary referral to another specialist can be arranged for adequate treatment and follow up.

Although the experiences of patients and relatives at our own ICU clinic are positive, there is currently a lack of evidence for the effectiveness of follow-up clinics [56,57]. In the UK, at least one planned randomized controlled trial will evaluate the effect of follow-up clinics on health-related quality of life and psychopathology [58]. Cost-effectiveness will be addressed in this study. There is no conclusive evidence on the best timing for follow up at post-ICU clinics. Theoretically the best time is when persistent symptoms are severe enough to be identified as forming an impairment for the patient, but can also be treated effectively with a minimal delay in treatment. To identify this point in time, knowledge of ICU sequelae and normal recovery is essential. Although evidence is lacking on this subject, we feel that a visit to the clinic one to two months after discharge from hospital may meet these conditions.

Conclusions
Critical illness and intensive care admission both cause physical and psychological morbidity which may persist for years and lead to functional limitations in daily life and diminished quality of life. This relationship is probably multifactorial and results from the critical illness itself, state of health before admission to intensive care, as well as from treatment and stay in the ICU.

Further research is clearly warranted to identify additional sequelae and to reveal causal mechanisms, which can lead to adjustments in care to prevent the occurrence of these sequelae. Awareness of the problems faced during rehabilitation is growing. The number of ICU outpatient clinics is increasing. Outpatient clinics could improve follow up of intensive care patients and treatment of sequelae, although further research is needed to confirm their effectiveness.

Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<td>ICU</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<td>ARDS</td>
<td>Adult respiratory distress syndrome</td>
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<td>CIPM</td>
<td>Critical illness polyneuropathy</td>
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<td>CIP</td>
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<td>CIM</td>
<td>Critical illness myopathy</td>
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<td>PTSD</td>
<td>Post-traumatic stress disorder</td>
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<td>HADS</td>
<td>Hospital Anxiety Depression Scale</td>
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<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>ADL</td>
<td>Activities of Daily Living</td>
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<td>IADL</td>
<td>Instruments Activities of Daily Living</td>
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References