

# **Depression and Anxiety Disorders in End-Stage Renal Disease Patients in Dialysis**

**Valjbona T. Preljevic, MD**

**Institute of Basic Medical Sciences**

**Department of Behavioral Sciences in Medicine**

**University of Oslo**

**In collaboration with**

**Institute of Clinical Medicine, University of Oslo**

**Department of Nephrology, Department of Research and Development**

**Division for Mental Health and Addiction,**

**Oslo University Hospital,**



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## Preface

The present thesis is based on the papers listed below, which are referred to in the text by Roman numerals in brackets.

### List of papers:

- I. Valjbona Tiric Preljevic, Tone Brit Hortemo Østhus, Leiv Sandvik, Christine Bull Bringager, Stein Opjordsmoen, Inger Hilde Nordhus, Ingrid Os, Toril Dammen  
**Psychiatric Disorders, Body Mass Index and C-reactive Protein in Dialysis Patients**  
Gen Hosp Psychiatry 2011; 33: 454-61.
- II. Valjbona Tiric Preljevic, Tone Brit Hortemo Østhus, Leiv Sandvik, Stein Opjordsmoen, Inger Hilde Nordhus, Ingrid Os, Toril Dammen  
**Screening for Anxiety and Depression in Dialysis Patients: Comparison of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory**  
J Psychosom Res 2012; 73:139-44.
- III. Valjbona Tiric Preljevic, Tone Brit Hortemo Østhus, Ingrid Os, Leiv Sandvik, Stein Opjordsmoen, Inger Hilde Nordhus, Toril Dammen  
**Anxiety and Depressive Disorders in Dialysis Patients: Association to Health Related Quality of Life and Mortality**  
Gen Hosp Psychiatry 2013; 35:619-24

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## Abbreviations

AUC	Area under the (ROC) curve dette bør være på rett linje
BDI	Beck Depression Inventory
BMI	Body mass Index (kg/m <sup>2</sup> )
CBB	Christine Bull Bringager
CCI	Charlson comorbidity Index
CMCI	Charlson modified comorbidity Index
CKD	Chronic kidney disease
CDI	Cognitive Depression Index
CI	Confidence interval
CRP	C-reactive protein
DSM	Diagnostic and Statistical Manual of Mental Disorders
DA	Depressive comorbid with anxiety disorder
ESRD	End-stage renal disease
GAD	Generalized anxiety disorder
GFR	Glomerular filtration rate
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale, Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale, Depression subscale
HD	Hemodialysis
HR	Hazard ratio
HRQOL	Health – related quality of life
ICD-10	International Classification of Diseases, 10 <sup>th</sup> edition
MCS	Mental component summary score
NOS	Not otherwise specified
NPV	Negative predictive value
NRR	Norwegian Renal Registry
NS	Non significant
OR	Odds ratio
PCS	Physical component summary score
PD	Peritoneal dialysis
PPV	Positive predictive value
PTSD	Post-traumatic stress disorder
QOL	Quality of life
ROC	Receiver operating characteristics
RT	Renal transplantation
RRT	Renal replacement therapy
SCID-I	Structured Clinical Interview for <i>DSM-IV</i> , Axis I disorders
SD	Standard deviation
SPSS	Statistical package for social sciences
SF36	Short Form-36 health survey
TD	Toril Dammen

## Summary

Depression and anxiety are highly prevalent conditions among physically ill patients, but ones that are often underdiagnosed and untreated.

The aims of this cross-sectional and prospective study of end-stage renal disease patients (ESRD) in dialysis (n=109) from four dialysis units in Norway, were to identify the prevalence of depression, anxiety and somatoform disorders, as well as the relationship between these disorders, biological markers, health-related quality of life (HRQOL) and mortality. We intended to identify screening tools with adequate psychometric properties, which could assist clinicians in identifying patients at high risk for depression and anxiety in dialysis patients. The present study was part of a larger study assessing HRQOL in dialysis patients from 10 different dialysis units. The Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale (HADS) and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV) (SCID-I) were applied. HRQOL was assessed using the Medical Outcome Short Form 36 (MOS SF-36). Information regarding socio-demographic, clinical and laboratory data were collected from the hospital records and the clinical report form.

Data on the time of death and time of renal transplantation were collected from the Norwegian Renal Registry (NRR). In the survival analysis, data were censored for transplantation. The median follow-up time for the prospective part of the study was 3.8 years (range 2.8-4.5 years), and none of the patients were lost to follow-up.

The results showed that approximately one-third of the patients had a current psychiatric disorder (depression 22%, anxiety 17%, somatoform disorders 1%, comorbid depression and anxiety disorders 8.3%), and that the prevalence of psychiatric disorders did not differ

between the two dialysis modalities, hemodialysis (HD) and peritoneal dialysis (PD). Patients with psychiatric disorders reported more impairment on six of eight HRQOL dimensions than those without psychiatric disorders. Our study revealed a lower prevalence of anxiety and somatoform disorders in dialysis patients than that reported in previous studies, although this was not the case for depression.

Psychiatric comorbidity was associated with C-reactive protein (CRP)  $\geq 6$  mmol/L and body mass index (BMI)  $\leq 21$  kg/m<sup>2</sup>.

Both BDI and HADS performed acceptably as screening instruments for depression, and at cut-off scores commonly used in clinical practice for depression screening (HADS-D  $\geq 8$ ; BDI  $\geq 16$ ), the BDI performed slightly better than the HADS-D. The optimal screening cut-off score for depression was  $\geq 7$  for the HADS depression subscale (HADS-D),  $\geq 14$  for the HADS total,  $\geq 11$  for the Cognitive Depression Index (CDI) and  $\geq 17$ , for the BDI, while the optimal screening cut-off score for anxiety was  $\geq 6$  for the HADS anxiety subscale (HADS-A).

Patients with only depressive disorders reported a more impaired HRQOL than for those without depressive disorders in four of eight SF-36 subscales. Additionally, patients with a depressive disorder and anxiety disorder (DA) reported more impairment compared to those without any psychiatric disorder in all SF-36 subscales. The survival analysis did not indicate that patients with depressive or anxiety disorders had a higher mortality than patients without such disorders.

In conclusion, we found in the present study that depressive and anxiety disorders were prevalent in dialysis patients and were associated with an impaired HRQOL, but not associated with dialysis modality or an increased risk of death. The prevalence of somatoform disorders was low, and strong correlations were found among psychiatric comorbidity, CRP and BMI. This may indicate that further psychiatric assessments should be given to dialysis

patients with a CRP  $\geq 6$  mmol/L and a BMI  $\leq 21$  kg/m<sup>2</sup>, such as screening for depression and anxiety.

Dialysis patients with comorbid depression and anxiety (DA) reported the most serious HRQOL impairment. Consequently, both depression and anxiety disorders should be assessed, as together they significantly contribute to HRQOL impairment.

# 1. Introduction

This thesis focuses on depressive, anxiety and somatoform disorders in patients with end-stage renal disease (ESRD) in dialysis treatment.

To help sustain their life, dialysis patients are dependent on time-consuming treatment that usually takes several times during the week. The use of pharmaceutical agents and restrictions on nutritional and fluid intake are also important, both for survival and improved general health. Reduced physical function and a hampered working ability may also present an additional burden for dialysis patients (1).

Various explanations of what may initiate and maintain depression and anxiety in ESRD patients have been proposed (2-15). Some patients may have greater vulnerability than others for the development of psychiatric disorders as a response to significant losses (16-18), such as loss of health, loss of independence or autonomy due to the treatment regime, loss of self-esteem due to a lack of working capability and reduced social contacts due to time consuming treatment. Anxiety is a common reaction to a life threatening illness (11, 19), and anxiety disorders have been shown to complicate comorbid diagnoses in patients with medical illness (4, 20, 21). Nevertheless, considering the high prevalence in dialysis population (22), research on anxiety disorders has received less attention than depressive disorder (23). Furthermore, a diagnosis of depression and anxiety can be difficult to assess, as physical symptoms may overlap symptoms associated with ESRD, and effective screening instruments have not been identified.

Moreover, data are scarce with regard to the prevalence of somatoform disorders in dialysis patients. Somatoform disorders are physical symptoms that patients may present that cannot be explained by any known medical condition (24, 25), and are also common disorders in

medical patients that frequently co-occur with depression and anxiety in a large proportion of these patients (26).

In order to provide good treatment, it is crucial to estimate the prevalence of depressive/anxiety/somatoform disorders, examine their associations to HRQOL impairment and identify effective screening instruments for psychiatric disorders in these patients.

## 1.1. End-stage renal disease (ESRD)

### 1.1.1. Definition, epidemiology and prognosis

ESRD is defined as chronic kidney failure with a glomerular filtration rate (GFR) below 15 ml/min/1.73 m<sup>2</sup>. Patients with a GFR below 15 ml/min/min/1.73 m<sup>2</sup> may need dialysis or kidney transplantation (renal replacement therapy, RRT) to maintain their health or life (17, 27). Chronic kidney disease (CDK) is defined on the basis of either GFR values below 60 ml/min/1.7 m<sup>2</sup> or kidney damage (28, 29) (Table 1).

**Table 1: Staging of chronic kidney disease**

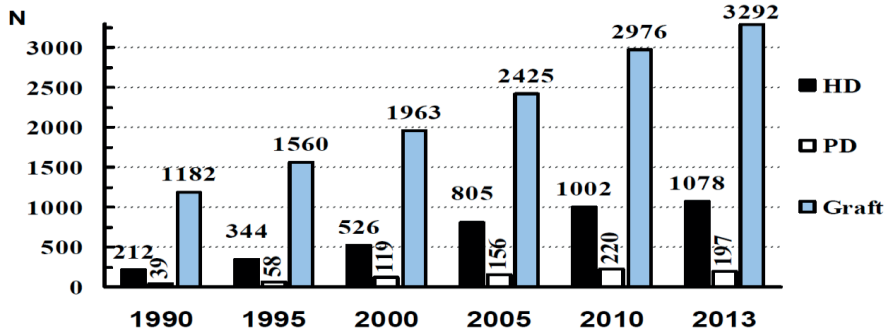
Stage	GFR	
1	>90 ml/min/1.73m <sup>2</sup> ;normal or high	Requires kidney damage*
2	60-90 ml/min/1.73m <sup>2</sup> ;mildly decreased	Requires kidney damage*
3	30-60 ml/min/1.73m <sup>2</sup> ;moderately decreased	
4	15-30 ml/min/1.73m <sup>2</sup> ;severely decreased	
5	< 15 ml/min/1.73m <sup>2</sup> or in dialysis	

\*Kidney damage is defined as the pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests (i.e. proteinuria , hematuria) or abnormalities using imaging techniques.

By the end of 2013, 4567 prevalent CKD patients in Norway received either dialysis treatment or lived with the renal graft, i.e. 899.4 per million inhabitants (30). This represents an increase of 113 patients of 2.5% since 2012.

# Renal replacement therapy in Norway

Treatment mode prevalence: 1990, -95, 2000, -05, -10 & -13



TL 05.14

It was less pronounced in dialysis than previously predicted (31) due to an increased transplantation rate. Hypertension and diabetes are the main causes for the need of RRT in Norway, while glomerulonephritis, interstitial nephritis and polycystic renal disease contribute to a lesser extent (30-33).

The increasing prevalence of hypertension, diabetes, and aging populations contribute to the increased number of patients with ESRD and in need of renal replacement therapy such as dialysis (34, 35).

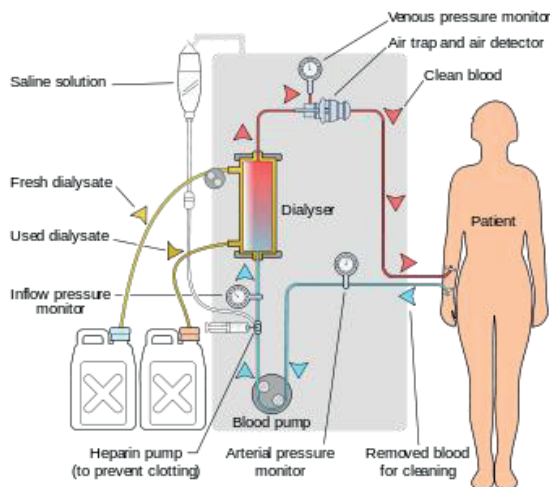
## 1.1.2. Treatment

Treatment of ESRD patients aims to enhance survival, with the options being hemodialysis, peritoneal dialysis and renal transplantation. Patients may transfer from one modality to another during their lifetime, but renal transplantation is considered the optimal treatment, both with regard to survival and quality of life. The initiation of RRT depends upon clinical symptoms, electrolyte abnormalities and fluid overload, as well as a consideration of GFR, which is usually below 10 ml/min/1.73m<sup>2</sup>.

### 1.1.2.1. Hemodialysis (HD)

More than one million patients worldwide receive HD treatment, which usually lasts for four hours and is performed three times weekly, most often in hospital-based units. Studies have shown that an increased frequency of dialysis may improve treatment efficiency and outcome (15, 36). In Norway more than 65% of patients started with hemodialysis as an initial RRT modality in 2013 (30). Figure 1 illustrates HD which is an extracorporeal therapy aimed at removing uremic waste products and excess fluid, correcting electrolyte disturbances and normalizing pH. The treatment requires a high blood flow that is obtained through an established vascular access (usually with an arteriovenous fistula or a permanent double-lumen intravenous catheter), which allows blood to be pumped into the dialyzer at a speed of 250-300 ml /min.

Figure 1: Hemodialysis (from <http://en.wikipedia.org/wiki/Dialysis>, 06.20.2014)

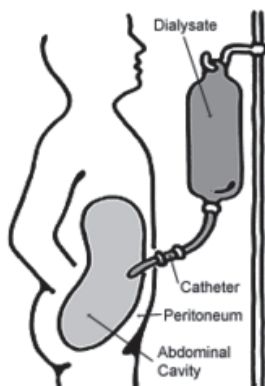




### 1.1.2.2. Peritoneal dialysis (PD)

PD is less frequently used than HD, using the patient's peritoneum as a dialysis membrane. The dialysis fluid is instilled into the peritoneal cavity through a permanent catheter and is usually exchanged every six-eight hours. The electrolyte- and glucose-containing dialysis fluid in the peritoneal cavity is exchanged during various time intervals, and uremic waste products (diffusion) and excess fluid (osmosis) are removed from the capillaries into the peritoneal cavity. This treatment can be administered by the patients in their own home after appropriate training. All patients are informed about this treatment option, but a few may not be able to do the procedures on their own, while others can not use this treatment due to medical conditions, e.g. gross obesity, severe lung disease, peritoneal adhesions or hernias. Because this is a continuous treatment that takes place both during day and night, the fluid and electrolyte shifts are less pronounced than during HD, and therefore have less of an impact on hemodynamic stability. Furthermore, PD preserves residual renal function better, which is important for the patient's survival and quality of life. In Norway, approximately 21% of patients in need of RRT initiated peritoneal dialysis in 2013(30), Figure 2 illustrating PD.

Figure 2: Peritoneal dialysis (from <http://en.wikipedia.org/wiki/Dialysis>, 06.20.2014)



### **1.1.2.3. Renal transplantation**

Renal transplantation (RT) is the optimal treatment for patients with ESRD, with improved survival rate, improved HRQOL and even the most cost-effective in the long run (37).

Although preemptive RT is possible, particularly when a living donor is available, most patients will spend some time in dialysis. There are few absolute contraindications for renal transplantation; however, many patients are not suitable due to serious medical conditions, particularly cardiovascular diseases, severe cognitive dysfunction or advanced cancer.

Furthermore, there is a shortage of organs for transplantation. The renal transplantation activity is very high in Norway (38) compared to other countries. In 2013 the median time on the waiting list for RT was six months. For patients receiving a renal graft from a deceased donor the median waiting time in 2013 was 9 months (31). During this period, 12% of all patients who initiated treatment for RRT were transplanted, and it has been reported that in Norway almost all patients <65 years on a waiting list received a transplant within four years after the start of RRT (38).

## **1.2. Depression, anxiety and somatoform disorders in ESRD patients**

### **1.2.1. Depression**

Depression is characterized by low mood, loss of interest and pleasure in activities, diminished energy, concentration difficulties and low self-esteem, feeling of guilt, disturbed sleep and appetite, and it is also sometimes accompanied with serious symptoms such as suicidal thoughts or plans. Depression can lead to functional impairment, reduced HRQOL, increased health-care utilization and mortality (39, 40). Worldwide, depressive disorders

affect 3.2% of the general population per year, and during a typical lifetime the incidence is 12%.

Many studies suggest that psychological, biological and socioeconomic factors can lead to depression in ESRD/CDK patients (12, 18). Psychological risk factors in these patients may be changes in social roles and self-image, a decreased autonomy and control, a loss of freedom, hopelessness, productivity and social involvement, a negative body image, low self-esteem, fear of an uncertain future, changes in existential questions and the meaning of life (1, 12).

Biological factors may include uremic toxins, chronic inflammation, disturbance of glucose-insulin homeostasis, deregulation of HPA axis and other biological mechanisms that lead to changes in neuro-hormonal activity (18). Additionally, demographic and socioeconomic risk factors such as younger age, female gender, low perceived social support, unemployment and low income may also play a role. Thus, there are several risk factors that may play a significant role in the development and maintenance of depression in dialysis patients.

Previous studies in ESRD patients have reported depression rates of 22–60% (41-45). The variability in prevalence rates may be related to differences in sample characteristics, varying definitions and assessment tools used across the studies (22, 26, 46, 47).

In most studies, the prevalence of depression in ESRD patients has been assessed by self-report questionnaires of depressive symptoms such as the Beck Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS).

The most commonly applied questionnaire for the assessment of depressive symptoms is the BDI (32, 41, 42). This inventory assesses both somatic and psychological aspects of depression. Moreover, neurovegetative symptoms of depression, including fatigue, cognitive deficits, decreased appetite, insomnia and loss of libido may occur secondarily to chronic renal failure, and in the absence of a depressive syndrome. Additionally, conditions associated

with ESRD such as uremia, anemia, diabetes and electrolyte disturbances may mimic depressive symptoms (7, 18, 19). As a result, BDI may overestimate depressive symptoms in ESRD patients. In order to diagnose a depressive disorder, the application of a diagnostic system based on categories, such as the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) is required. The DSM-IV defines the criteria for diagnosing depressive disorders. Table 2 shows the diagnostic criteria for major depression and dysthymia.

**Table 2. DSM IV\* criteria for major depression and dysthymia**

#### **DSM-IV criteria for major depression**

**A.** Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

**Note:** Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- (1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
- (2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
- (3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
- (4) insomnia or hypersomnia nearly every day
- (5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
- (6) fatigue or loss of energy nearly every day
- (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- (8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
- (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

**B.** The symptoms do not meet criteria for a Mixed Episode.

**C.** The symptoms cause clinically significant distress or impairment in social, occupational, or

other important areas of functioning.

**D.** The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

**E.** The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

#### **DSM-IV criteria for dysthymia**

**A.** During a majority of days for 2 years or more, the patient reports depressed mood or appears depressed to others for most of the day. When depressed, the patient has 2 or more of:

- Appetite decreased or increased
- Sleep decreased or increased
- Fatigue or low energy
- Poor self-image
- Decreased concentration and decisiveness
- Feels hopeless or pessimistic

**B.** During this 2 year period, the above symptoms are never absent longer than 2 consecutive months.

**C.** During the first 2 years of this syndrome, the patient has not had a Major Depressive Episode.

**D.** The patient has not had any Manic Hypomanic or Mixed Episodes.

**E.** The patient has never fulfilled criteria for Cyclothymic Disorder.

**F.** The disorder does not exist solely in the context of a chronic psychosis (such as Schizophrenia or Delusional Disorder).

**G.** The symptoms are often not directly caused by a general medical condition or the use of substances, including prescription medications.

*\*Diagnostic and Statistical Manual of Mental disorders, Fourth Edition*

Before our study was conducted, only two previous studies had applied DSM criteria for the diagnosis of depressive disorder in dialysis patients (39, 48). These studies suffered from methodological limitations, such as only being conducted in a single dialysis center, a lack of inclusion of patients representative of dialysis patients in general (limited sample size, >70% non-Caucasians, no PD patients). Neither the level of depressive symptoms nor the prevalence of depressive disorder had previously been assessed in Norwegian dialysis patients.

*In summary*, there was a need to assess the prevalence of depressive disorder with structured diagnostic interviews applying diagnostic criteria in clinically representative dialysis patients.

### **1.2.2. Anxiety**

Anxiety is a natural emotion to a stressful situation. Even so, it is classified as an anxiety disorder when the exaggerated worries and symptoms interfere with the patient's work /school/social function and family life. Anxiety disorders may also affect work productivity, function and health-care costs (23).

DSM-IV describes criteria for diagnosing anxiety disorders, discriminating among the following anxiety disorders: generalized anxiety disorder, panic disorder with or without agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder.

The diagnostic criteria are presented in Table 3:

**Table 3. DSM IV\* criteria for anxiety disorders**

#### **Generalized Anxiety Disorder**

Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least six months, about a number of events or activities (such as work or school performance).

The person finds it difficult to control the worry.

The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). Note: Only one item is required in children.

restlessness or feeling keyed up or on edge  
being easily fatigued  
irritability  
muscle tension  
difficulty falling or staying asleep, or restless unsatisfying sleep  
difficulty concentrating or the mind going blank

Symptoms can also include nausea, vomiting, and chronic stomach aches.

The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being away from home or close relatives (as in Separation Anxiety Disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during post-traumatic stress disorder.

The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder.

### **Panic disorder with (or without) agoraphobia:**

#### **A. Both (1) and (2):**

1. recurrent unexpected panic attacks
2. at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
  - persistent concern about having additional attacks
  - worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
  - significant change in behavior related to the attacks

#### **B. The presence (or absence) of agoraphobia**

**C.** The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).

**D.** The panic attacks are not better accounted for by another mental disorder

## **Social Phobia**

**A.** A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing.

**B.** Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic attack.

**C.** The person recognizes that the fear is excessive or unreasonable.

**D.** The feared social or performance situations are avoided or else are endured with intense anxiety or distress.

**E.** The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

**F.** In individuals under age 18 years, the duration is at least 6 months.

**G.** The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder

**H.** If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it, e.g., the fear is not of stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behavior in Anorexia Nervosa or Bulimia Nervosa.

Specify if: Generalized: if the fears include most social situations (also consider the additional diagnosis of Avoidant Personality Disorder)

## **Obsessive Compulsive Disorder**

### **Obsessions**

Recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and that cause marked anxiety or distress.

The thoughts, impulses, or images are not simply excessive worries about real-life problems.

The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action.

The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind, and are not based in reality.



## **Compulsions**

Repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.

The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts are not actually connected to the issue, or they are excessive.

In addition to these criteria, at some point during the course of the disorder, the individual must realize that his/her obsessions or compulsions are unreasonable or excessive. Moreover, the obsessions or compulsions must be time-consuming (taking up more than one hour per day), cause distress, or cause impairment in social, occupational, or school functioning.<sup>[4]</sup> OCD often causes feelings similar to those of depression.

## **Post traumatic Stress Disorder**

- A. Exposure to a traumatic event
- B. Persistent reexperience (e.g. flashbacks, nightmares)
- C. Persistent avoidance of stimuli associated with the trauma (e.g. inability to talk about things even related to the experience, avoidance of things and discussions that trigger flashbacks and reexperiencing symptoms fear of losing control)
- D. Persistent symptoms of increased arousal (e.g. difficulty falling or staying asleep, anger and hypervigilance)
- E. Duration of symptoms more than 1 month
- F. Significant impairment in social, occupational, or other important areas of functioning (e.g. problems with work and relationships.)

*\*Diagnostic and Statistical Manual of Mental disorders, Fourth Edition*

A need for studies among ESRD patients that apply a structured diagnostic interview for psychiatric disorders has been emphasized (4, 11, 22) because most previous studies in dialysis patients have only used self-report and clinical rated only, anxiety scales . Anxiety symptoms are common in dialysis patients, but are less studied than those of depression (4,

22, 46). Taskapan and colleagues (19) reported a prevalence of 30% for at least one anxiety disorder using Primary Care Evaluation of Mental Disorder (PRIME-MD), and to the best of our knowledge only one previous study has used the Structured Clinical Interview for DSM-IV, Axis I disorders (SCID-I) for the diagnostic assessment of anxiety disorders in HD patients. The authors reported a prevalence of 27% (4) and a need for further studies of anxiety disorders in both HD and PD patients.

Anxiety often co-occurs with depression; however, this is often overlooked in both clinical and research settings (4, 20). Due to the fact that their symptoms may overlap with those of renal disorders, the detection of comorbid depression and anxiety may present a diagnostic challenge in dialysis patients (2, 4, 49). It has been shown that anxiety is a risk factor for the development of depression (50). Consequently, there is a need to study to what degree anxiety occurs alone or as a comorbid condition with depression in ESRD patients. To the best of our knowledge again, no previous study on anxiety and depression in ESRD patients has estimated the prevalence of comorbid anxiety and depression and their association with outcomes such as HRQOL and mortality.

*In summary*, few previous studies have assessed anxiety in dialysis patients and those suffering from limited sample sizes, non-representative patient samples and a lack of reliability estimates of the diagnosis. Hence, there is a need to estimate the prevalence of anxiety disorders and anxiety comorbid to depression in a more methodologically sound study, and to explore the associations between anxiety disorders and HRQOL and mortality in dialysis patients.

### 1.2.3. Somatoform disorders

Some patients may present physical symptoms that cannot be explained by any known medical condition, i.e. medically unexplained or functional somatic symptoms or somatoform disorders (24, 51). Patients with somatoform disorders report somatic symptoms that are either very distressing or result in a significant disruption of functioning and an over-utilization of health services (51). Usually, they suffer from excessive and disproportionate thoughts, feelings and behaviors regarding those symptoms (52), as the severity of somatoform disorders may range from mild to severe and chronic. Somatoform disorders include somatization disorders, undifferentiated somatoform disorder, hypochondriasis, conversion disorder, pain disorder, body dysmorphic disorders and somatoform disorder not otherwise specified. The DSM-IV criteria for somatoform pain disorder are presented below in Table 4.

**Table 4. DSM IV\* criteria for somatoform pain disorder**

#### **Somatoform pain disorder**

Pain which causes significant distress or impairment in functioning which cannot be fully explained by a physician. It must be judged to be related to psychological factors and cannot be better explained by another disorder.

#### Diagnostic criteria:

- A. Pain in one or more anatomical sites the predominant focus of the clinical presentation and is of sufficient severity to warrant clinical attention..
- B. The pain causes clinically significant distress, impairment, or both in social, academic, occupational, or other important areas of functioning.
- C. Psychological factors are judged to play an important role in the onset, severity, exacerbation, or maintenance of the pain.
- D. The pain is not intentionally produced or feigned.
- E. The pain is not better accounted for by a mood disorder, anxiety disorder, or psychotic disorder and does not meet criteria for dyspareunia..

*\*Diagnostic and Statistical Manual of Mental disorders, Fourth Edition*

Somatoform disorders are prevalent (25, 53), persistent, disabling and costly in patients with medical illnesses (24).

There is also insufficient knowledge concerning the prevalence of somatoform disorders in dialysis patients. We are aware of only one previous study (19) that has assessed somatoform disorders in dialysis patients, which reported a prevalence of 33% using the Primary Care Evaluation of Mental Disorder, an instrument that is designed for use in primary care (54). The results of this study suggest that somatoform disorders are prevalent; nonetheless, the study only comprised 40 HD patients, and the reliability of these diagnoses was not reported (19).

Furthermore, studies in medically ill patients with comorbid anxiety and depression have shown significantly higher number of medically unexplained physical symptoms compared to medically ill patients without psychiatric disorders (55). Because we hypothesized that anxiety and depression were commonly occurring in the present study, there was also a need to estimate the prevalence of somatoform disorders.

*In summary*, there is a limited amount of evidence with regard to the occurrence of somatoform disorder in dialysis patients. There is therefore a need to determine the prevalence of various somatoform disorders in patients with ESRD by applying a structured clinical interview such as SCID-I.

### **1.3. Association between biological markers and depression and/or anxiety**

Previous studies have shown that negative emotions such as depression and anxiety are associated with increased inflammatory markers in patients both with and without somatic comorbidity (56-58). There is some evidence on the association between depression and/or

anxiety and biological markers in dialysis patients. The presence of comorbid depression in dialysis patients has been associated with elevated serum C-reactive protein (CRP), elevated ferritin concentrations, hypoalbuminemia and anemia (59). Malnutrition and inflammation are prevalent in dialysis patients, leading to the so-called malnutrition–inflammation syndrome (60). Depression contributes to an increased risk of inflammation (61) in patients without somatic comorbidity.

*In summary*, there is limited evidence in support of these correlations, we aimed to investigate the potential associations between the presence of psychiatric comorbidities (anxiety and/or depression) and nutrition and inflammation parameters in ESRD patients.

#### **1.4. Screening instruments for depression and anxiety in ESRD patients**

Although the negative impact of depression and anxiety in dialysis patients has been emphasized to some degree, these conditions are still underdiagnosed and untreated (22, 62). The detection of psychiatric disorders is important in order to provide effective treatment and reduce the additional negative impact of these disorders.

The gold standard for diagnosing psychiatric disorders is a structured clinical interview, e.g. such as the SCID-I. However, the SCID-I requires administration by trained health professionals, is time-consuming and is difficult to apply in routine clinical practice. Reliable, valid and easily applicable screening instruments are needed to help identify those ESRD patients with anxiety and depression disorders that require further follow-up and treatment.

##### **Screening for anxiety and depression**

A self-report questionnaire, the BDI, has been frequently used to assess depressive symptoms in dialysis patients (32, 40). Screening for depression is complicated because of overlapping

symptoms between depression and uremia per se (49). The BDI comprises psychological, cognitive and somatic items, though somatic symptoms can be prevalent in dialysis patients, without necessarily being part of a depression or anxiety disorder. Therefore, the Cognitive Depression Index (CDI), a truncated version of the BDI without the somatic items of depression, has been suggested in order to help reduce the possible confounding between symptoms of medical illness and the somatic components of depression as measured by the BDI (40, 63, 64). To the best of our knowledge, the cut-off score of  $CDI \geq 12$  and how this correlates with a *DSM-IV* diagnosis of depressive disorder and a comparison with the screening properties of other instruments, for example BDI or HADS-D, has not been previously assessed in dialysis patients.

The HADS has been reported to perform well in assessments of symptom severity of anxiety and depression in general (65). In order to avoid the confounding of symptoms from underlying somatic diseases, this questionnaire only contains psychological questions. Generally speaking, the use of the HADS as an instrument for the assessment of anxiety and depression in the somatic, psychiatric and general populations has shown a good performance at the recommended cut-off value of  $\geq 8$  (65). However, the utility of the HADS as a screening tool for anxiety disorders in dialysis patients has been addressed (4), thus the need to study HADS as a screening instrument for anxiety disorders and depression in these patients seems warranted.

There is a lack of knowledge of the screening properties of HADS, BDI and CDI in dialysis patients; therefore, we aimed to describe and compare the screening properties of HADS, BDI and CDI for anxiety and depression in dialysis patients by using a structured diagnostic interview (SCID-I) as the gold standard.

### **1.5. Health-related quality of life (HRQOL)**

HRQOL comprises physical, psychological (including emotional and cognitive) and social functioning (66). Dialysis patients often have severe comorbidity, e.g. cardiovascular disease, which may affect HRQOL and reduce life expectancy (67, 68). These patients are faced with serious stressors related to their illness, associated comorbidity and the complex medical treatment. They may also have restrictions in food and fluid intake, and experience symptoms such as itching, dyspnoea, pain, restless legs, sleep disturbances and fatigue, as well as psychosocial stressors such as loss of work and autonomy and depressive and anxiety symptoms (12, 69). Several studies have reported that HRQOL is substantially impaired in dialysis patients compared to the general populations (32, 70-73). When compared to patient populations with other chronic illnesses, such as diabetes, chronic pulmonary diseases, rheumatic diseases and cardiovascular diseases, HRQOL also seems especially compromised in dialysis patients (74, 75).

It is important to identify the factors that contribute to a low HRQOL in these patients.

Depressive symptoms are frequent in ESRD patients treated with dialysis, and may adversely affect HRQOL (32, 47, 68, 76). However, anxiety symptoms and disorders are less studied in ESRD patients, and their impact on HRQOL is largely unknown.

Sareen and co-workers showed strong associations between anxiety disorders and comorbid physical conditions, poor quality of life and disability (20). Only one previous study in dialysis patients has studied the association between anxiety disorders and HRQOL and reported anxiety disorders to be associated with a negative impact on quality of life to a higher degree than that of depression (11).

Hence, there is limited knowledge of the associations between HRQOL and anxiety disorders alone, and anxiety disorder comorbid with depression in dialysis patients.

## **1.6. Mortality**

The annual mortality rate in dialysis patients is approximately 21% (77), and the main causes of death are cardiovascular diseases (78, 79). Non-adherence to hemodialysis, dietary restrictions and excessive interdialytic fluid weight gain are all risk factors for premature death (80). Refusing treatment or committing suicide is also a reason for premature death in international studies in this population group (78). The impression is that this is rare in Norwegian dialysis population as the likelihood to receive a renal graft is high in Norway, but data are lacking (oral communication Professor Ingrid Os).

### **1.6.1. Depression and mortality in ESRD patients**

A recent Swedish study (81) compared the mortality in patients with CKD stages 4 and 5, dialysis- and in transplanted patients and matched general population controls. This study reported that mortality was by far the highest in patients in dialysis compared to the other groups (CKD and transplantation group) and the general population (81). Patients in dialysis may have high rates of depressive disorders (22), with the associations between depression and mortality being contradictory. Early studies applied self-reported measures of depressive symptoms (40), i.e. the BDI (82) or the HADS (83). Independent associations between depressive symptoms and mortality were observed in HD patients, with higher levels of depression being associated with an increased risk of mortality (83). Other studies have failed to show any associations between depression and mortality in dialysis patients (84-86). The reasons for the discrepancy in the results may be various assessment methods of depression or differences in duration of the follow-up time.

Only one previous study has studied the association of depressive disorders and mortality in dialysis patients (39) applying the SCID-I instrument. A significant association between depressive disorders and a combined measure of hospitalization and mortality was reported.



However, the association between the depressive disorder and mortality alone was not reported. Additionally, we are not aware of any previous study that has assessed associations of anxiety disorders and mortality in dialysis patients.

*In summary*, studies of associations between depression and mortality have yielded contradictory results, and did not include anxiety. Consequently, there is a need to study the association between depressive and anxiety disorders as assessed with SCID-I and mortality in ESRD patients.

## **2. Aims of the study**

Given the background, the more specific objectives of the various papers comprising this study were:

- To estimate the prevalence of depressive, anxiety and somatoform disorders according to dialysis modality in Norwegian dialysis patients (Paper I).
- To compare dialysis patients with and without psychiatric comorbidity regarding clinical characteristics, health-related quality of life (HRQOL) and markers of nutrition and inflammation (Paper I).
- To explore and compare the screening properties of the HADS and BDI in the identification of anxiety and depressive disorders in dialysis patients (Paper II).
- To examine the associations between depressive/anxiety disorders, perceived HRQOL and mortality in dialysis patients (Paper III).

### **3. Material and Methods**

#### **3.1. Study design**

This preplanned study was based on data from a cross-sectional, multicenter study of dialysis patients in Norway (Papers I, II, III). The dialysis patients were followed for three-four years with respect to mortality after censoring for renal transplantation (Paper III).

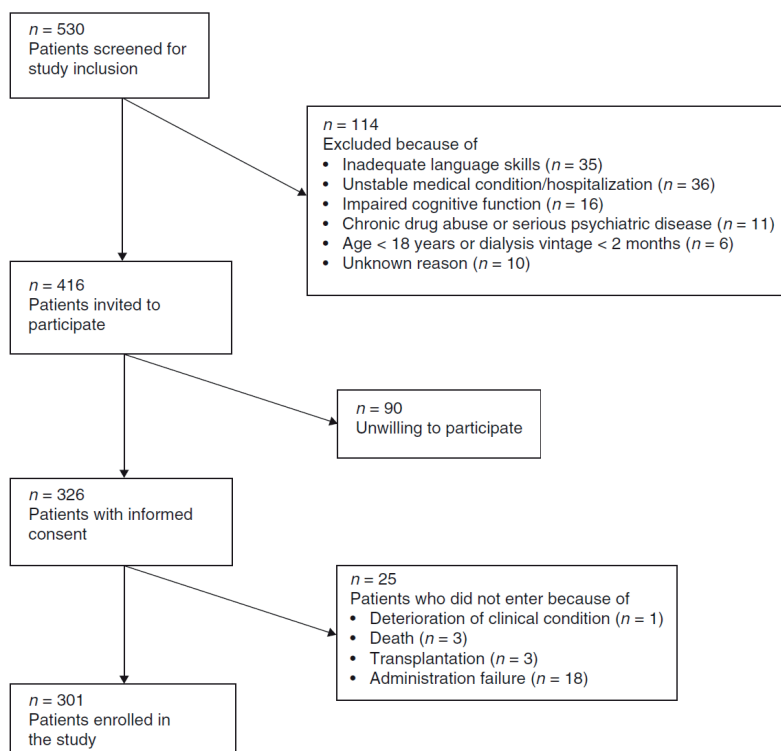
#### **3.2. Study sample**

The study focused on psychiatric disorders assessed by the SCID-I as part of a larger multicenter study (32) that comprised dialysis patients from 10 different hospitals (five university- and five regional hospitals). These hospitals provide renal health care for both a rural and urban population, with a flow chart of the recruitment process of the multicenter study, of which this preplanned sub-study is a part, shown in Figure 3.

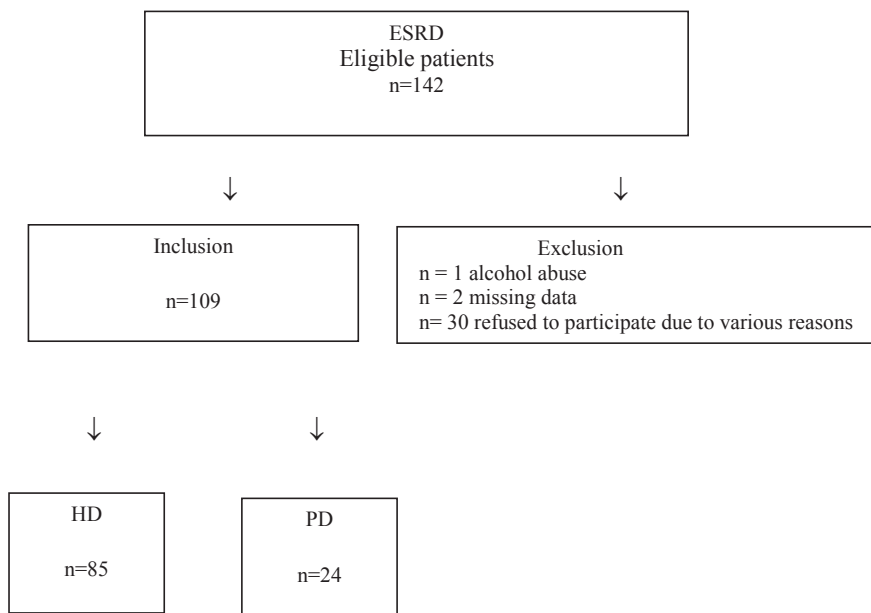
The larger multicenter study comprised 301 participants who were consecutively enrolled in the study from August 2005 to February 2007. Because of administrative reasons (only resources to conduct psychiatric interviews in four centers), this preplanned study of psychiatric disorders comprised patients from four of the 10 dialysis centers in various hospitals (two university hospitals and two regional hospitals) from different parts of Norway (Oslo University Hospital Ullevål, Haukeland University Hospital, Vestfold Regional Hospital and Buskerud Regional Hospital). A total of 142 dialysis patients at the four study centers were evaluated for participation in this study, which included an assessment with a SCID-I interview, with 111 consenting (an enrollment rate of 78% of those eligible), whereas 30 declined to participate in the sub-study (not having time, tiredness, refusal without explanation). Two interviews were lost because of administrative failure, and these patients were excluded from the analysis, and one patient was also excluded due to alcohol abuse.

Hence, the total sample comprises 109 patients (a participation rate of 77% of those eligible, 36% of total study sample).

**Figure 3: Flowchart of the recruitment process in the main study (32)**



**Figure 4: Flowchart of the recruitment process in the four centres in the current study**



### **3.3. Recruitment procedure**

Inclusion and exclusion criteria:

**The inclusion criteria were:**

- PD or HD
- Age > 18 years
- Dialysis for > two months

- Clinically stable condition during the last four weeks prior to the investigation
- Adequate Norwegian language skills
- Signed informed consent after oral and written information

**The exclusion criteria were:**

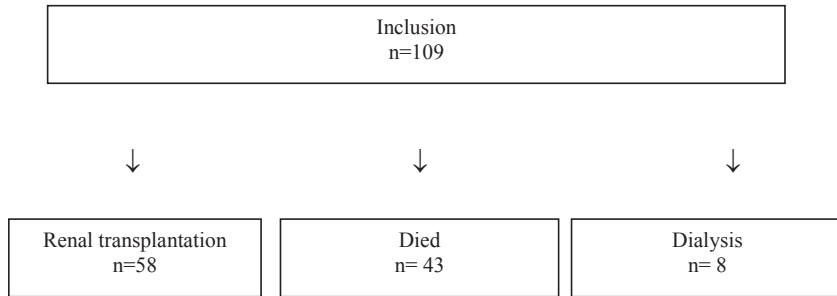
- Serious cognitive dysfunction, psychosis or drug/alcohol abuse. The cognitive dysfunction was assessed by the clinical judgment made by the dialysis staff.
- Presence of intercurrent disease requiring hospitalization (pneumonia, peritonitis or other infectious diseases, sepsis, cardiac or cerebral events, elective surgical procedures); the patients were excluded from study participation until at least four weeks after discharge from the hospital.

### **3.4. Follow-up**

Data were retrieved from the Norwegian Renal Registry (NRR) up to January 2010. The follow-up time ranged from 2.8 to 4.5 years, with a median of 3.8 years. During follow-up, 43 patients (39.4%) died, while 58 (53.2%) dialysis patients received a renal transplant.

Based on BDI, patients who were on the transplantation waiting list did not differ regarding depressive symptoms from those that were not on the list (87).

**Figure 5: Flow chart of the follow-up (Paper III)**



### **3.5. Assessments**

#### **3.5.1 Demographic and clinical variables**

##### **3.5.1.1. Demographic variables**

The clinical report form included both sociodemographic and clinical data retrieved from hospital charts and direct questioning. Demographic data included age, gender, marital status, education and work status.

##### **3.5.1.2. Clinical data**

Clinical data included the cause of ESRD, dialysis modality, dialysis vintage and comorbidities.

##### **3.5.1.3. Assessment of laboratory data**

Laboratory data were collected from the hospital charts. Hemoglobin, CRP and total cholesterol were all obtained from routine blood sampling undertaken at the time of the study

inclusion (within a one-month timeframe). The body mass index was calculated as body weight (kg) (weight was measured predialysis for HD patients, and for PD patients without dialysate fluid in the peritoneal cavity)/height (m)<sup>2</sup>.

Demographic, clinical and laboratory data are presented in Table 5.

#### **3.5.1.4 The Charlson Comorbidity Index (CCI)**

The CCI, which is a composite score of 17 comorbid conditions and age, was used to assess the severity of somatic comorbidity. Comorbid conditions were attributed, with scores ranging from 1 to 6. A score of 1 was added for each decade above 40 years of age (for example: a 52-year-old patient with coronary artery disease and AIDS gets a score of 8 based on the CCI). In this study, we also used the CCI without entering age into the calculations, the so-called the Charlson Modified Comorbidity Index (CMCI). The comorbid somatic disorders included in the CCI are presented in Table 5. The CCI includes conditions that were not relevant in our study, e.g. dementia.

**Table 5. Charlson Comorbidity Index**

Somatic disorders (n=17)	Score for comorbidity
Coronary artery disease	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disorder	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia	2
Severe renal disease	2
Diabetes with end-organ damage	2
Tumours, leukaemia, lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumour	6
AIDS	6



### **3.5.2. Psychiatric assessments**

#### **3.5.2.1. Psychiatric interview**

##### **Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV) for Axis I disorders (SCID-I.**

The Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (88) was used to establish psychiatric diagnoses. The interview was administered by an experienced research psychiatrist Toril Dammen (TD) who was unaware of the medical history and scores on all self-report questionnaires, though not of dialysis modality. The participants were evaluated for the current psychiatric disorders: depressive, anxiety and somatoform disorders.

Assessments were conducted during HD dialysis sessions in an effort to standardize the assessment procedure and the time point relative to dialysis treatment. In PD patients, the interviews were performed in accordance with the patients' routine outpatient appointments. Psychiatric comorbidity was defined as the presence of at least one anxiety disorder and/or one depressive disorder. Anxiety disorders were defined as at least one current (within the past month) anxiety disorder: generalized anxiety disorder, social phobia, agoraphobia, panic disorder with or without agoraphobia, posttraumatic stress disorder, obsessive-compulsive disorder or an anxiety disorder not otherwise specified. Depressive disorders were defined as current (criteria met in the past month) major depression, minor depression or dysthymia according to the DSM-IV criteria. Somatoform disorders were defined as current somatization disorder, hypochondrisis disorder or pain disorder.

##### **Interrater reliability**

Most interviews were audiotaped, and in order to establish interrater reliability 25 randomly selected tapes were scored independently by another experienced psychiatrist, who was blind to the results of the first rater. Reliability was established for the categories of any depressive

disorder as either present/absent and any anxiety disorder as present/absent. The interrater reliability score for depressive disorder was excellent, with  $\kappa = 1$ , and for anxiety disorder moderate, with  $\kappa = 0.6$ . A discussion of interrater reliability follows in section 5.1.4.1, page 55.

### **3.5.2.2. Self-report measures**

#### **Beck Depression Inventory**

The BDI is a 21-item, self-report instrument; each item is scored 0-3, with total scores ranging from 0 to 63, in which higher scores indicate a higher severity of depressive symptoms (89). This instrument includes psychological, cognitive and somatic items, with the BDI having been used in studies of dialysis patients (40, 42).

#### **Cognitive Depression Index**

The somatic items of the BDI may be associated with the severity of medical disease, although high levels of endorsement for these somatic items could confound somatic depression factors with the symptoms of medical illness. In order to control for the possible confounding contribution of somatic symptoms due to medical illness or treatment effects, the CDI comprising 15 BDI items was generated in order to only evaluate psychological symptoms (63, 90). The last six items of the BDI scale are somatic (fatigue, sleep, sexual dysfunction, disordered appetite and changes in weight and general health), and these are not included in the CDI (90).

#### **Hospital Anxiety and Depression Scale**

The HADS is a 14-item self-report questionnaire, each item is scored from 0-3, with seven items comprising the anxiety subscale (HADS-A) and seven items comprising the depression

subscale (HADS-D) (91). It has demonstrated good psychometric properties and is effective in assessing anxiety and depressive symptoms in patients with various medical diseases and in the general population, according to a literature review (65). Recommended cut-off scores are  $\geq 8$  on each subscale for doubtful cases and  $\geq 11$  for definite cases, and  $\geq 15$  and  $\geq 19$  on the HADS total, respectively (91) .

### **3.5.3. HRQOL assessment**

#### **3.5.3.1. The Medical Outcomes Study Short Form (MOS SF) 36**

The Medical Outcome Study (MOS) 36-item short form (SF-36) is a self-administered generic questionnaire that assesses the following eight domains of HRQOL, including physical functioning, physical role (role limitations due to physical health), bodily pain, general health, vitality, social functioning, emotional role (role limitations due to emotional problems) and mental health (92). From the eight domains were derived two component summary scales: the physical component summary scale (PCS) and the mental component summary scale (MCS).

A score between 0 and 100 was calculated for each domain, with a higher score indicating a perception of better health. The Norwegian version of the MOS SF-36 has also been validated (92).

### **3.5.4. Procedure**

In order to standardize the use of assessment instruments in the multicenter study, informative lectures about the study were held for the staff at all study centers prior to data collection. One or two nurses from each dialysis center attended a seminar at Oslo University Hospital, Ullevål, including lectures and more detailed information about the aims and methodology of the study. All the research nurses had experience from clinical work with dialysis patients.

Self-report questionnaires were applied in a standardized sequence during the dialysis treatment for HD patients, as well as during the routine outpatient control for PD patients. The SCID-I was conducted by the research psychiatrist (TD) after the participants had filled in the questionnaires, with the representativity of the sample discussed in section 5.1.3, page 54.

### **3.6. Statistical analyses**

#### **3.6.1. Sample size calculation**

Based on the results of previous studies, we assumed that 20% of the patients would be diagnosed with a depressive disorder, and that the screening instrument (BDI) would classify 25% of the patients as “depressed.”

For example a realistic result (22) in such a study will be that 11 of the truly depressed patients will be classified as “depressed” by the screening method, and that 14 of the truly not depressed patients will be classified as depressed by the screening instrument. Thus, sensitivity and specificity will be 56% and 92%, respectively. It may be further shown that 95% confidence intervals for these estimates will be 36-76% and 85-97%, respectively. The lengths of these intervals are indicators of the precision of estimates, and because we consider these precisions to be acceptable, we decided to include at least 100 patients in our study.

Comment: The suggested estimates for sensitivity and specificity are obviously rather arbitrary. However, it may be shown that with other realistic estimates the confidence interval lengths will be similar to for those presented above.

In descriptive analyses, continuous data were presented as means  $\pm$  SD or median with inter-quartile range if appropriate (skewed data), whereas categorical data are presented as percentages.

When comparing continuous variables in two groups, an independent samples *t* test was used if distribution was normal; otherwise a Mann–Whitney test was used. The chi-squared test, or Fisher exact test when appropriate, was used to compare categorical variables. A one-way analysis of variance (ANOVA) with a post-hoc Bonferroni adjustment or Kruskal-Wallis test for skewed data were also used to compare continuous variables in more than two groups. Analyses were performed using statistical package SPSS, version 16 (SPSS, Chicago, IL, USA).

### **3.6.2. Logistic multivariate analysis (Paper I)**

Socio-demographic and clinical variables were selected for multivariate analyses. When the aim was to identify variables associated with psychiatric morbidity (PM), logistic regression analyses were used, with PM as a dependent variable. This selection procedure was performed in two steps. In Step 1, each variable was included one-by-one in the regression analyses. In Step 2 all the variables that were significant in Step 1 were included simultaneously as independent variables in the regression analyses. Variables being significant in Step 2 were declared as variables associated with PM. The following variables were evaluated: Hb, albumin, cholesterol, age, gender and dialysis duration, CCI, Kt/V, BMI and CRP. In this model, the strength of the associations is presented as odds ratios (OR) with 95% confidence intervals.

### **3.6.3. Sensitivity and specificity calculations (Paper II)**

Sensitivity (detecting a diagnosis of depression/anxiety when present), specificity (indicating a lack of depressive/anxiety diagnosis when not present), positive predictive value (PPV) and negative predictive value (NPV) were all calculated for various cut-off scores for each of the investigated instruments. An agreement between the instruments (BDI, HADS) and the categorical DSM-IV diagnoses was measured using kappa coefficients, while the area under

(AUC) the receiver operating characteristic curve (ROC) was used as a measure of diagnostic precision. A ROC curve area of 1 indicates perfect diagnostic precision, whereas an area of 0.5 indicates a complete lack of precision. A maximal discrimination between those with or without a DSM- IV diagnosis was reached at the highest sum of sensitivity and specificity (the Youden Index) (93).

#### **3.6.4. Survival analyses (Paper III)**

Survival time was defined as the time from entry into the study until death. Otherwise, survival time was defined from entry until observation time (December 31, 2011) or transplantation.

Survival was analyzed using Kaplan-Meier plots. The association between depression/anxiety and mortality were estimated with a Cox Regression Analysis, entering only depression/anxiety as an independent variable, and then adjusting for somatic comorbidity, dialysis duration, gender and age. The results from the Cox Regression Analysis are presented as hazard ratios (HR) with 95% confidence intervals (CI).

#### **3.7. Ethical aspects**

The study protocol was approved in June 2005 by the National Committee for Medical and Health Research Ethics in Norway, and concession was obtained from the National Data Inspectorate.

At the dialysis units, all patients who were eligible for inclusion in the study received oral and written information about the study. This information and the written consent form emphasized that study participation was voluntarily, and that non-participation would have no impact on further investigations or treatment.

A trained psychiatrist conducted the SCID interviews, which contained questions that may have caused distress in some patients. The interviewer was therefore sensitive to the patients' responses. None of the patients reported distress during the interview or wanted to terminate the SCID interview. The patients for which a major depression disorder was diagnosed, and if the patient was in need for treatment he/she was referred to the doctor responsible for the treatment, or the general practitioner was informed after the patient's approval.

## 4. Summary of papers

### Paper I

#### **Psychiatric disorders, body mass index and C-reactive protein in dialysis patients**

**Objective:** The objective of the study was to identify the prevalence of depression, anxiety and somatoform disorders in dialysis patients according to dialysis modality and to compare dialysis patients with and without psychiatric comorbidity regarding clinical characteristics, health-related quality of life (HRQOL) and markers of nutrition and inflammation.

**Methods:** One hundred and nine patients were assessed for depression, anxiety and somatoform disorder with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. The Short Form 36 was used for assessment of HRQOL. Sociodemographic, clinical and laboratory data were collected.

**Results:** About one third, 30.3%, had a current psychiatric disorder regardless of dialysis modality (depressive disorder, 22%; anxiety disorder, 17%; somatoform disorders, 1%), and these reported more impairment on HRQOL dimensions than patients without psychiatric comorbidity. In the multivariate analysis significant correlations between psychiatric comorbidity and CRP $\geq$ 6 mmol/L [odds ratio (OR), 3.6; 95% confidence interval (CI), 1.3–9.9;

P=.015] and body mass index (BMI  $\leq 21$  kg/m<sup>2</sup>) (OR, 4.2; 95% CI, 1.4–12.7; P=.011) were observed.

**Conclusion:** Depressive and anxiety disorders were common in this sample of dialysis patients and were associated with impaired HRQOL, while prevalence of somatoform disorders was low. A strong correlation between psychiatric comorbidity, CRP and BMI indicates that special attention should be given to patients with CRP $\geq 6$  mmol/L and BMI $\leq 21$  kg/m<sup>2</sup> followed with more thorough psychiatric evaluation.

## Paper II

### Screening for anxiety and depression in dialysis patients: comparison of the hospital anxiety and depression scale and the beck depression inventory

**Objective:** Although anxiety and depression are frequent comorbid conditions in dialysis patients, they remain underrecognized and often untreated. The aim of the study was to evaluate the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI) and a truncated version of the BDI, the Cognitive Depression Index (CDI), as screening tools for anxiety and depression in dialysis patients.

**Methods:** A total of 109 participants (69.7% males), from four dialysis centers, completed the self-report symptom scales HADS and BDI. Depressive and anxiety disorders were diagnosed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). The sensitivity, specificity, positive and negative predictive value, overall agreement, kappa and receiver operating characteristic (ROC) curves were assessed.

**Results:** Depressive disorders were found in 22% of the patients based on the SCID-I, while anxiety disorders occurred in 17%. The optimal screening cut-off score for depression was  $\geq 7$  for the HADS depression subscale (HADS-D),  $\geq 14$  for the HADS-total,  $\geq 11$  for the CDI and



≥17 for the BDI. The optimal screening cut-off for anxiety was ≥6 for the HADS anxiety subscale (HADS-A) and ≥14 for the HADS-total. At cut-offs commonly used in clinical practice for depression screening (HADS-D: 8; BDI: 16), the BDI performed slightly better than HADS-D.

**Conclusion:** The BDI, CDI and HADS demonstrated acceptable performance as screening tools for depression, as did the HADS-A for anxiety, in our sample of dialysis patients. The recommended cut-off scores for each instrument were: ≥17 for BDI, ≥11 for CDI, ≥7 for HADS depression subscale, ≥ 6 for HADS anxiety subscale and ≥14 for HADS total. The CDI did not perform better than the BDI in our study. Lower cut-off for the HADS-A than recommended in medically ill patients might be considered when screening for anxiety in dialysis patients.

### **Paper III**

**Anxiety and depressive disorders in dialysis patients: association to health related quality of life and mortality.**

**Objective:** To examine the associations between depressive/anxiety disorders, perceived Health-Related Quality of Life (HRQOL) and mortality in dialysis patients.

**Methods:** Patients were assessed for depressive and anxiety disorders with the Structured Clinical Interview for DSM-IV. The HRQOL was assessed with the Medical Outcome Short Form 36 (MOS SF-36), and the Beck Depression Inventory and Hospital Anxiety and Depression Scale were also applied. Sociodemographic, clinical and laboratory data were also collected.

**Results:** Patients with depressive disorders reported more impaired HRQOL on four of the eight subscales, while those with a depressive disorder comorbid with anxiety disorder (DA) reported more impairment on all MOS SF-36 subscales compared to those without any

psychiatric disorder. During the observation period, 50% of those with depressive disorder, 28% of those with anxiety disorder and 33% of patients with both (DA disorder) died. A survival analysis did not indicate that patients with depressive or anxiety disorders had a higher mortality than patients without such disorders.

**Conclusion:** Dialysis patients with depressive disorders reported impaired HRQOL, whereas those with anxiety disorders did not. Patients with DA reported the most serious HRQOL impairment. No evidence was obtained to support the hypothesis that depressive and anxiety disorders contributed to compromised survival in dialysis patients. In patients with depressive disorder, anxiety disorders should also be assessed as they significantly contribute to impaired HRQOL.

## **5. Discussion**

### **5.1. Methodological considerations**

#### **5.1.1. Study design**

In the present study, cross-sectional and prospective designs were used. Prospective data on mortality and on renal transplantation were obtained from the Norwegian Renal Registry, with the follow-up time ranging from 2.8 to 4.5 years.

#### **5.1.2. Internal validity**

We intended to study all patients who fulfilled the inclusion criteria as described in section 3.3, and recruitment procedures were implemented in collaboration with the physicians and staff of each dialysis unit. We are not aware of any systematic bias in registration or approach of eligible patients that may have affected the sample characteristics or outcome measures. However, we did not apply a control procedure to ensure that all potential eligible patients were registered and approached for study participation.

Østhus et al (94) has thoroughly discussed a sample bias that concerns all participants who were screened for study inclusion in the main study (n=530) (see Figure 3, page 34), as she compared the characteristics of participants (n=300) with non-participants (n=230). There was a clinical impression during patient inclusion that those who consented to participate in the main study presented as healthier than those who declined study participation. The most common reasons that were verbally stated by the non-participants for refusing to participate were exhaustion and a lack of motivation, which may be symptoms of depression. Based on this observation, Østhus et al (94) concluded that the results of the main study concerning HRQOL impairment and levels of depression may be underestimated due to a response bias in favour of more motivated and less exhausted patients consenting to participate.

One patient with alcohol abuse according to DSM-IV was excluded, but no patients were excluded because of psychosis or severe cognitive impairment.

Our substudy was performed in four study centers that were chosen because of practical reasons. However, in order to assess whether patients who agreed to participate in the substudy (n=109) differed from the participants in the main study, we compared the characteristics of the patients in the study who did not undergo SCID I interviews (n=191) with those who did in the substudy (n=109) (Table 6). The substudy participants had significantly lower levels of hemoglobin and higher levels of albumin. We consider the differences to be small and of little clinical importance. Furthermore, the substudy participants were less likely to be married and retired, and more likely to be separated and disabled. Being separated and disabled are characteristics associated with a higher risk for psychiatric disorders (95), which might have led to a higher prevalence of psychiatric disorders in our sample. Nonetheless, we did not find significant differences between substudy participants and non-participants with regard to scores on measures of

depression, anxiety and psychological distress as assessed by BDI, HADS-D, HADS-A and HADS-T, respectively (Table 6).

In conclusion, although participants differed from non-participants on some variables (marriage status, disabilities), this was not reflected in the scores of anxiety and depression.

<b>Table 6: Sociodemographic and clinical variables for all dialysis patients, participants and non-participants.</b>				
	Total study sample n = 300	Non-participants n = 191	Participants n = 109	P – value*
Age, years	59.8 ± 16.2	61 ± 16.5	57.8 ± 15.7	0.101
Female gender, %	34	36.1	30.3	0.314
<b>Marital status</b>				
Single, %	14.7	12.6	18.3	0.081
Married or cohabitant, %	64.2	67.9	57.8	<b>0.002</b>
Divorced or separated, %	9.7	7.9	12.8	<b>&lt;0.001</b>
Widowed or widower, %	11.4	13.1	11.0	0.118
<b>Education</b>				
0-7 years, %	24.4	23.8	27.1	0.573
>7-12 years, %	51.3	50.9	51.4	0.94
>12 years, %	24.4	25.2	21.4	0.52
<b>Workability</b>				
Able to work, %	12.8	13.3	11.0	0.600
Disabled, %	50.0	42.4	71.2	<b>&lt;0.001</b>
Retired, %	37.2	44.3	17.8	<b>&lt;0.001</b>
<b>Primary renal disease</b>				
Vascular / hypertensive kidney disease	26.3	28	23.3	0.412
Glomerulonephritis	20.9	22.7	17.7	0.373
Diabetic nephropathy	13.8	12.1	16.8	0.295
Others	38.8	37	42	0.457
<b>Clinical characteristics</b>				
Peritoneal dialysis, %	19.3	17.3	22.9	0.287
Time on dialysis, months	15.5 ± 14.9	16.2 ± 15.4	14.3 ± 13.8	0.304
Hemoglobin, g/dl	12.1 ± 1.5	12.3 ± 1.3	11.9 ± 1.7	<b>0.030</b>
S-Iron	12.0 ± 4	11.9 ± 5.7	12.1 ± 5.0	0.812
Albumin g/L	38.2 ± 4.9	37.8 ± 5.2	38.9 ± 4.2	<b>0.049</b>
CRP mmol/L	6 (2-13.0)	7(2.1-13.0)*	6 (2-12.6)*	0.875
Total cholesterol mmol/L	4.2 ± 1.3	4.2 ± 1.4	4.3 ± 1.1	0.617
SBP, mmHg	141.4 ± 21.5	140 ± 19.7	144.6 ± 24.5	0.085
DBP, mmHg	77.5 ± 12.6	76.0 ± 12.4	80.3 ± 12.8	0.011
BMI, kg/m <sup>2</sup>	24.9 ± 4.8	24.9 ± 4.6	24.9 ± 5.3	0.981
KTV	1.3 ± 0.3	1.4 ± 0.2	1.3 ± 0.3	0.190
<b>Comorbidity</b>				
CCI	6.4 ± 2.5	6.5 ± 2.6	6.1 ± 2.4	0.156
CMCI without age	3.9 ± 1.7	4.0 ± 1.8	3.8 ± 1.6	0.328

BDI	11.4±7.9	10.8±7.3	12.4±8.8	0.134
HADS-A	4.7±4.1	4.6±4.2	4.9±4.0	0.518
HADS-D	4.9±3.8	4.7±3.8	5.2±3.9	0.939
HADS-T	9.6±7.3	9.4±7.3	10.1±7.2	0.927

Data are presented as means ± SD unless otherwise stated; \*P-value for the difference between SCID and non-SCID participants; **CCI** Charlson comorbidity index; **CMCI** Charlson modified comorbidity index; BDI Beck Depression Inventory; HADS-A Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D Hospital Anxiety and Depression Scale- Depression subscale; HADS-T Hospital Anxiety and Depression Scale,\*Median (25%-75%).

**SBP**-Systolic blood pressure; **DBP**-Diastolic blood pressure, **BMI**-Body mass index

The participation rate in this substudy was 78%. Furthermore, in order to assess for sample bias among those who were asked to participate in this substudy (n=142), we compared participants (n = 109) with non-participants (n = 33) regarding age, gender and levels of depressive and anxiety symptoms based on BDI and HADS scores. We found a significant difference only for gender (more men among the participants than non-participants). Based on this finding, we explored whether there was an association between gender and presence of an anxiety- or depressive disorder in our study, but did not find such an association. Hence, we conclude that there we have not identified evidence supporting that the difference in gender affected the prevalence estimates of anxiety and depression in the present study.

In conclusion, we consider the participation rate in the substudy to be satisfactory, and without selection biases that could have affected the prevalence rates of psychiatric disorders in the present sample.

### 5.1.3. External validity

We studied dialysis patients admitted to several centres, and implemented few exclusion criteria in order to be able to assess a representative sample of dialysis patients in Norway.

We included both HD and PD patients.

The majority of patients in RRT in Norway are males (67.4% [www.nephro.no](http://www.nephro.no) ) with a median age of 66.5 years, ranging from 0.4 to 90.9 years. The mean age, gender and etiology for ESRD of the investigated sample was quite similar to what has been reported in The Norwegian Renal Registry's Annual Report 2013 and in most international studies (22, 39). The participants in our study were almost all Caucasians, so our results may therefore not be applicable to non-Caucasians. In Norway, there is a high transplantation rate (38) that affects the total amount of time spent on chronic dialysis, and may thus represent a potential for selection bias compared to dialysis patients in other countries with a lower transplantation rate and a longer duration of dialysis treatment. However, we do not know of any study on an association between the amount of time spent in dialysis and psychological distress. Consequently, the implication of a potential selection bias in our study is unclear. *In summary*, our conclusion is that our results cannot necessarily be generalized to countries outside of Norway.

#### **5.1.4. Assessments**

##### **5.1.4.1. Psychiatric assessments**

###### **Diagnostic assessments**

Psychiatric diagnoses were assessed using the SCID interview for Axis I disorders. The SCID-I interview yields highly reliable diagnoses of Axis I disorders (88), and is often considered to be the gold standard of diagnostic assessments in clinical research. However, the results of reliability estimates in one study may not be generalized to other studies. As described in section 3.4.2.1, we estimated the kappa for the agreement between the presence and absence of at least one anxiety disorder or one depressive disorder.

In order to avoid any bias towards a higher prevalence of disorders in patients with a previously established psychiatric diagnosis, or for those who scored high for

depression and anxiety symptoms on the self-report questionnaires, such information was not available for the interviewer or the second rater. The interrater reliability score for a depressive disorder was defined as excellent, with  $\kappa = 1$ , and for anxiety disorder it was defined as moderate, with  $\kappa = 0.6$  according to definitions by Viera et al. (96). The moderate reliability of the diagnosis of anxiety disorders was primarily explained by differences regarding whether the diagnosis of a generalized anxiety disorder was present or absent based on differences in the interpretation of the criterion of excessive worry. Consequently, anxiety disorders and GAD in particular seem to be more difficult to evaluate because the criteria for these disorders may be more difficult to reliably interpret and assess. Nevertheless, we do not know to what extent raters agree across research groups, e.g. whether the presence or absence of GAD or anxiety disorders in our group differed from diagnostic evaluations conducted by other research groups in this field (4, 19, 41). Furthermore, we do not know if reliability estimates of anxiety disorders in our study differ from those in other studies, as two studies did not report interrater reliability estimates (19, 41), while Cukor et al. reported an overall excellent agreement between raters regarding both anxiety and depression ( $\kappa = 0.94$ ) (4), but did not specifically report estimates for anxiety disorders.

Regarding the dimension of somatoform disorders, only the symptom dimension of pain was assessed. Therefore, information about other potential somatoform symptoms such as bowel symptoms and dizziness were not assessed.

The SCID-I was administered by a single research psychiatrist, and was always administered at a defined time point in relation to dialysis in a routine clinical setting. The moderate reliability for anxiety disorders was a limitation of this study, thereby suggesting that the reliability of anxiety disorders should be assessed and attended to in future studies

#### **5.1.4.2. Self-reported questionnaire**

In general, we applied questionnaires that are frequently used in dialysis studies with authorized translations into Norwegian, and preferably with Norwegian normative data.

#### **BDI**

Complete responses were obtained from 91 patients (83%), and no participants had five or more missing items. If less than five BDI item responses were missing, these were substituted for by the most frequent occurring item score from the total study sample on that particular item. Two of the patients did not fill in the BDI questionnaire, but still participated in the SCID –I interview. These were excluded from the screening test analyses. As assessed through the use of Cronbach's  $\alpha$ , the internal consistency for the BDI in the present study was 0.86.

#### **HADS**

A complete HADS score was obtained from 104 patients (95%). Two patients responded to 50% of the items, and these were excluded from all screening analyses. If one item response was missing, this was substituted by the most frequently occurring item score from the total study sample on that particular item. By performing this procedure, we obtained scores from 107 participants.

The Cronbach's  $\alpha$  in the present sample for HADS were HADS total: 0.88, HADS-A: 0.86 and HADS-D: 0.80, which is considered as satisfactory (97).



## **SF-36**

Complete SF-36 scores were obtained from 105 patients, and missing data were substituted for according to the scoring algorithm of SF-36. By doing this, we obtained scores from 105 patients. SF-36 contained national normative Norwegian data from the general population.

### **5.1.4.3. Comorbidity assessment**

#### **Charlson's Comorbidity Index**

We obtained scores from all the participants. The scores were obtained from a scoring sheet scored by the dialysis personnel based on journal data, and all responses were thoroughly reviewed by two researchers (VP and TBØ). The scores were obtained by consensus, and the instructions provided by the creator of the scale were accurately followed.

### **5.1.4.4. Laboratory and clinical assessment**

#### **CRP and BMI**

C-reactive protein was obtained from the monthly routine blood sampling, with the last one taken before study participation.

Body mass index was calculated from height and body weight (body weight was measured pre-dialysis for HD and for PD patients without dialysate fluid in the peritoneal cavity).

### **5.1.4.5. Summary of methodological considerations**

Due to the cross-sectional design, causal relationships cannot be inferred. Furthermore, cognitive deficit was assessed by clinical evaluations and not through the use of standardized screening tools. Regarding generalizability, we consider the data to be representative for the Norwegian dialysis population. Even so, caution should be exercised in generalizing our results to non-Caucasians and dialysis patients outside Norway.

Additionally, we have not assessed all somatoform disorders, but only those assessed by SCID-I. The moderate reliability of the diagnosis of anxiety disorders was mainly explained

by differences regarding whether a diagnosis of generalized anxiety disorder was present or absent because of the differences in the interpretation of the criterion of excessive worry. Our limited sample size for each disorder did not allow for an analysis of separate depressive- or anxiety disorder diagnoses due to a lack of statistical power.

The strengths of our study include the use of structured clinical interviews according to DSM-IV criteria, an excellent reliability of depression, a high participation rate and a patient sample that was representative of the general HD and PD dialysis population. Furthermore, the SCID-I was undertaken by a single investigator and was always administered at a defined time point in a routine clinical setting. All self-report scales had satisfactory reliability.

## 5.2. Results and clinical implications

### 5.2.1. Prevalence of psychiatric disorders and clinically significant symptoms

Overall, we found that anxiety and depression are commonly occurring in dialysis patients (Papers I and II), with the prevalence of psychiatric disorders shown in Table 7.

**Table 7: Prevalence of psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in patients treated with dialysis**

Total	
DSM-IV Diagnosis	n = 109
n (%)*	
<b>Anxiety disorders</b>	
Panic disorder	6 (5.5)
Social phobia	8 (7.2)
Posttraumatic stress disorder	2 (1.8)
Generalized anxiety disorder	5 (4.6)
Any current anxiety disorder	18 (16.5)

## Depression

Major depression	16 (14.7)
Dysthymia	4 (3.7)
Depressive disorder NOS	4 (3.7)
Any current depressive disorder	24 (22.0)

## Somatoform disorder

Pain disorder	1 (0.9)
Any current psychiatric disorder	33 (30.3)

NOS, not otherwise specified; \*Percentages do not add up to 100% because of psychiatric comorbid conditions

## Prevalence of depression

The comparison of the results of our study with the results of other studies that have assessed depressive disorders with a structured psychiatric diagnostic interview shows that the prevalence rates for depressive disorders were similar to- or somewhat lower than in most of those studies in which SCID –I was applied (24-29%) (22, 48,49) (Table 8).

**Table 8: Prevalence studies of depression in ESRD patients**

Author	Study year	Patient number	Assessment tool	Prevalence (%)	Depression; Symptoms or disorder
Taskapan et al. (19)	2005 Turkey	40 HD	PRIME-MD	35%	Depressive disorder
Watnick et al. (48)	2005 USA	62HD	SCID	26%	Depressive disorder
Cukor et al. (22)	2007 USA	70 HD	SCID	29%	Depressive disorder
Arenas et al. (98)	2007 Spain	75 HD	BDI≥10 BDI≥19 HDRS≥7 HDRS≥18	44% 15% 53% 23%	Depressive symptoms Depressive symptoms Depressive symptoms Depressive symptoms

Hedayati et al. (39)	2008 USA	52 HD	SCID	24%	Depressive disorder
Johnson & Dwyer (99)	2008 USA	103 HD	BDI $\geq$ 10	54%	Depressive symptoms
Grant et al. (100)	2008 UK	57 HD	Interview ICD-10 BDI $\geq$ 10	12% 56%	Depressive disorder Depressive symptoms
Kao et al. (101)	2009 Taiwan	861 HD	BDI $\geq$ 14	61%	Depressive symptoms
Senol et al. (102)	2010 Turkey	156 PD	BDI $\geq$ 17	42%	Depressive symptoms
Cengic et al. (103)	2010 Bosnia	200 HD	BDI $\geq$ 11	51%	Depressive symptoms
Garcia et al. (104)	2010 Brazil	47 HD	HDRS $\geq$ 7	68%	Depressive symptoms
Chilcot et al. (82)	2010 UK	160 HD,PD	BDI $\geq$ 16	25%	Depressive symptoms
Chen et al. (105)	2010 Taiwan	200 HD	M.I.N.I. HADS-D $\geq$ 8	25% 35%	MDD only Depressive symptoms
Bossola et al. (106)	2010 Italy	80 HD	BDI $\geq$ 14	53%	Depressive symptoms
Park et al. (107)	2010 Korea	160 HD	BDI $\geq$ 18	32%	Depressive symptoms
Riezebos et al. (83)	2010 The Netherlands	101 HD	HADS-D $\geq$ 7	42%	Depressive symptoms
Atalay et al. (108)	2010 Turkey	124 PD	BDI $\geq$ 17	26%	Depressive symptoms
Cruz et al. (109)	2010 Brazil	70 HD	M.I.N.I. BDI $>$ 11	10% 36%	Depressive disorder Depressive symptoms
Lopez et al. (110)	2010 Brazil	868 HD	CES-D $\geq$ 18 CES-D $\geq$ 16	44% 51%	Depressive symptoms Depressive symptoms
Prelejevic et al. (111)	2011 Norway	109 HD,PD	SCID BDI $\geq$ 17 BDI $\geq$ 16 BDI $\geq$ 15 BDI $\geq$ 14 BDI $\geq$ 10 HADS-D $\geq$ 8 HADS-D $\geq$ 7	22% 25% 27% 37% 41% 56% 25% 30%	Depressive disorder Depressive symptoms Depressive symptoms Depressive symptoms Depressive symptoms Depressive symptoms Depressive symptoms Depressive symptoms
Ferreira et al. (112)	2011 Brazil	130 HD	BDI $\geq$ 12	34%	Depressive symptoms
Ramirez et al. (113)	2011 Brazil	170 HD	HADS (cut-off unknown)	13%	Depressive symptoms
Feroze et al. (114)	2012 USA	170 HD,PD	BDI (cut-off unknown)	36%	Depressive symptoms
Reckert et al. (41)	2013 Germany	52 HD	SCID BDI $>$ 10 HADS-D $>$ 7	17% 33% 15%	Depressive disorder Depressive symptoms Depressive symptoms

Macaron et al. (115)	2013 Lebanon	51 HD	HADS-D>7	50%	Depressive symptoms
Silva Junior et al. (62)	2013 Brazil	148 HD	BDI≥10 BDI≥19 BDI>30	50% 42% 9%	Depressive symptoms
Hui Juan Ng et al. (116)	2014 Singapore	159 HD	HADS-D≥8	54%	Depressive symptoms
Turkistani et al. (117)	2014 Saudi Arabia	286 HD	HADS-D≥8	22%	Depressive symptoms

BDI: Beck Depression Inventory

SCID: Structured Clinical Interview for Diagnoses, HADS-D

HADS-D: Hospital Depression and Anxiety Scale

M.I.N.I.: Mini International Neuropsychiatric Interview

Interview according to ICD-10

However, one recent study from Germany (2013) showed a somewhat lower prevalence of depressive disorders assessed with SCID-I (17%) (41). Cukor et al. (22) reported a higher prevalence of depression (29%), compared to what we found (22%) in our study. The reason for the difference in the prevalence of depressive disorders may be due to different study population characteristics. Cukor et al. (22) included participants from one urban HD center with many current psychiatric comorbidities, including psychosis and drug abuse. We included HD and PD patients in four different dialysis centers from both rural and urban areas, while patients with psychoses and current drug abuse were excluded from our study. Hence, the participants in our study might have been less likely to suffer from anxiety and depressive disorders.

In our study, two-thirds of those with a depressive disorder suffered from major depressive disorders. Thus, 15% of the total sample suffered from MDD, which is slightly above the prevalence reported by Grant et al. (100) , who applied the ICD-10 criteria.

Studies with use of self-report questionnaires show generally a higher prevalence of significant depressive symptoms compared to studies with diagnostic interviews (Table 8).

When a BDI  $\geq 10$  was applied as a criterion for defining depression, we found a prevalence rate of 56%, which is in line with the results of most other, studies (50%-56%), but not as low as one study (33%) with a similar definition. Worth noting, the Center for Cognitive Therapy recommends the following cut-off point for mild to moderate depression: 10-18 (118).

The prevalence rates reported with the use of the BDI differ in various studies in dialysis patients, which is likely due to the application of different cut-off points in various studies.

The prevalence of clinically significant symptoms as assessed with HADS-D in our study was higher than that found in previous studies from Germany and Saudi Arabia, but similar to or lower than that reported from Taiwan (110), The Netherlands (87), Singapore (121) and Lebanon (120) (Table 8).

### **Prevalence of anxiety**

The comparison of the results of our study with those of other studies that assessed anxiety with a structured psychiatric diagnostic interview revealed the presence of a lower prevalence of anxiety disorders in our study (Table 9). Cukor et al. reported a prevalence of anxiety disorders of 27% in a one-centre study performed in an urban area of the USA (22). The reason for the discrepancy in prevalence rates between our study and others is most likely due to differences in the sample characteristics, as patients with current drug abuse and psychotic disorders were included in the studies by Cukor et al. In contrast, patients with these conditions were excluded from our study.

A recent German study from one dialysis centre (41) reported a 17 % prevalence of GAD assessed with SCID I, which was substantially higher than the 4.6% that we found in our study (Table 7). However, the German study did not apply interrater reliability assessments, and the diagnostic assessments were not performed by an experienced psychiatrist or psychologist. In our study, social phobia had the highest prevalence among anxiety disorders, reaching 7.2%. Table 9 shows the prevalence of anxiety disorders in dialysis patients:

**Table 9: Prevalence of anxiety in ESRD patients**

Author	Study year	Patient number	Assessment tool	Prevalence%	Anxiety
Taskapan et al. (19)	2005 Turkey	40 HD	PRIME -MD	30%	Anxiety disorder
Cukor et al. (22)	2007 USA	70HD	SCID	27%	Major anxiety disorder (Excluded specific phobia)
Arenas et al. (98)	2007 Spain	75 HD	HARS $\geq$ 6 HARS>15	47% 13%	Anxiety symptoms
Johnson & Dwyer (99)	2008 USA	103 HD	BAI $\geq$ 22	17%	Anxiety symptoms
Bossola et al (106)	2010 Italy	80 HD	HARS $\geq$ 6 HARS>15	48% 49%	Mild symptoms of anxiety Moderate/severe symptoms of anxiety
Preljevic et al. (111)	2011 Norway	109 HD, PD	SCID  HADS-A $\geq$ 8 HADS-A $\geq$ 7	17%  25% 32%	Major anxiety disorder (Excluded specific phobia) Anxiety symptoms Anxiety symptoms
Ramirez et al. (113)	2011 Brazil	170 HD	HADS (not reported cut-off)	26%	Anxiety symptoms
Feroze et al. (114)	2012 USA	155 HD	BAI (not reported cut-off)	53%	Anxiety symptoms
Reckert et al. (41)	2013 Germany	52 HD	SCID HADS-A>7	17% 23%	GAD only Anxiety symptoms
Macron et al. (115)	2013 Lebanon	51 HD	HADS-A>7	45%	Anxiety symptoms
Hui Juan et al. (116)	2014 Singapore	159 HD	HADS-A $\geq$ 8	45%	Anxiety symptoms
Turkistani et al. (117)	2014 Saudi Arabia	286 HD	HADS-A $\geq$ 8	23%	Anxiety symptoms

PRIME-MD: Primary Care Evaluation of Mental Disorders

SCID: Structured Clinical Interview for Diagnoses,

HADS-A: Hospital Depression and Anxiety Scale

BAI: Beck Depression Inventory

The Hopkins Symptom Checklist

Johnson and Dwyer (99) reported a low prevalence of clinically significant anxiety symptoms using BAI, though other studies that have used self-report questionnaires show a generally higher prevalence of anxiety symptoms. We found a prevalence of 32% with HADS-A $\geq$ 7,

which is higher than levels found in a study from Reckert et al. (41) but lower than the prevalence found in a study by Macaron et al. (115) (Table 9).

This is the first study to report comorbidity rates for anxiety and depression. Comorbid depression and anxiety were found in 8-9% of the patients. In addition, we found a high prevalence of anxiety disorders in those who suffered from a depressive disorder (37.5 %). This comorbidity rate is in line with other studies in psychiatric settings.

### **Prevalence of somatoform disorders**

The prevalence of somatoform disorders in our sample was 0.9 %, as only one patient suffered from somatoform pain disorder. None of the participants could be diagnosed with somatization disorder or hypochondriasis disorder. Our finding is substantially lower than in other studies conducted in patients with chronic medical conditions (25), one of which included dialysis patients (19) with somatoform disorders found in 33% of the patients. The explanation for this discrepancy could be differences in the assessment methods used. The assessment of somatoform disorders in the latter study was performed using the Primary Care Evaluation of Mental Disorder (PRIME-MD), which is a semi-structured interview that has been designed for use in primary care (54). This interview has different criteria than SCID-I, e.g. it comprises 15 potential somatoform symptoms and if one is scored as somatoform, a somatoform disorder is diagnosed. If three criteria are scored positively, a multi-somatoform disorder is registered. In comparison, SCID-I comprises more extensive criteria (DSM-IV) in order to diagnose a somatization disorder. The application of PRIME-MD in patients with both somatic and psychological complaints has been questioned because the test/retest reliability was not satisfactory ( $\kappa = 0.27$ ) in a study of such patients (127).

Another explanation of the low prevalence may be that the patients in our study were closely monitored regarding their health conditions. As a result, they may experience less



hypochondriacal concerns as compared to other medical patients with a less extensive treatment regimen.

### **5.2.2. Anxiety, depression and markers of nutrition and inflammation**

#### **CRP and BMI in dialysis patients**

There is evidence of a causal relationship between depression and the activation of the inflammatory response system in the general population (119); however, such a relationship is controversial in dialysis patients (120). CRP levels are often used as a marker of inflammation to examine the association between depression and inflammation in dialysis patients. The association between anxiety and the markers of inflammation is less studied compared to that of depression. We found that the majority of patients with depression and/or anxiety had higher levels of CRP compared to those without anxiety and depression. Our finding is in contrast with those that did not report a positive association between CRP and depression (82, 106, 107), but in line with those reported by Montinaro et al.(121) Dogan et al. (122), Kalender et al. (59), Simic et al. (120) and Ko et al. (123).

We found that dialysis patients with CRP levels  $\geq 6$  mmol/L and low BMI levels  $<21$  kg/m<sup>2</sup> had four times higher odds of having depression and/or anxiety disorder (Paper I). Because the majority of patients with depression and/or anxiety had elevated levels of CRP and low BMI, this may suggest a possible association between psychiatric comorbidity, inflammation and malnutrition. Malnutrition and inflammation are prevalent in dialysis patients, thereby leading to the so-called malnutrition–inflammation syndrome. Another previous study showed that depression contributed to an increased risk of infection (61), whereas depression has been linked to inflammation in other studies (120, 121) in ESRD patients. Furthermore, it has been shown that CRP levels and other immunological parameters decrease with antidepressant treatment in patients with major depression (108, 124).

A recent study showed a strong correlation between somatic comorbidity and CRP levels in dialysis patients (125). In our study, however, somatic comorbidity was not associated with the presence of psychiatric disorders; hence, somatic comorbidity cannot explain the elevated CRP levels in our patients with psychiatric disorders.

We did find an association between psychiatric comorbidity and low BMI, which is in accordance with the result that depression, was significantly associated with a low BMI compared with non-depressed patients in a study by Chen et al. (105) that evaluated 200 HD patients. However, others have failed to find such an association (118).

Reduced appetite and body weight are common symptoms of depression. We may speculate whether a low BMI operates as a starting point in the development of a psychiatric disorder by triggering an inflammatory response, thus rendering the dialysis patients more susceptible to depression or anxiety.

There are some limitations associated with the assessment of BMI that should be acknowledged. Smaller changes in BMI may result from changes in water balance that occur as a result of dialysis treatment.

Based on our findings, we suggest in conclusion that special attention regarding depression and anxiety should simultaneously be given to dialysis patients who exhibit a low BMI and high CRP levels. Whether treatment for depression and anxiety will improve nutritional status remains to be determined.

### **5.2.3. Screening properties of the HADS and BDI in the detection of depressive disorder and anxiety disorders**

Our main finding was that both HADS and BDI were acceptable screening instruments for depressive disorders (HADS-D, HADS-total, CDI and BDI) and HADS-A for anxiety disorder, with sensitivities  $> 0.80$  and specificities  $\geq 0.60$ . Our findings are in line with

Loosman et al. (89), who explored the screening properties of HADS and BDI and concluded that HADS demonstrated to be as good as the BDI in detecting depression in dialysis patients. According to the Youden Index (the highest sum for sensitivity and specificity), our results suggest that the use of lower cut-off values for HADS-A (value  $\geq 6$ ) would be more appropriate for screening than previous recommendations (value  $\geq 8$ ). In our study, we found that because of a low sensitivity at the recommended threshold ( $\geq 8$ ), HADS-A misses 40% of all patients with anxiety disorders. The HADS total had not satisfactory screening properties, performing best at a cut-off of 14 or more.

For screening purposes, a high sensitivity and NPV are most important, while for diagnostic sensitivity a high specificity and PPV are more essential. Our results are in contrast with a previous study (4) that assessed HADS-A as a screening tool for anxiety in dialysis patients, and concluded that HADS was not suitable for the screening of anxiety in dialysis patients.

Because there are only a few studies that have explored the screening properties of HADS-A in dialysis patients with the application of different methods of statistical analysis across studies, there is a need for further studies that explore this screening tool.

Regarding the screening for depression, we also found that the optimal cut-off value was higher for the BDI (value  $\geq 17$ ) than those reported in previous studies (value  $\geq 16$ ,  $\geq 15$ ,  $\geq 14$ ,  $\geq 13$ ) (42, 48, 89, 126). In our study we also assessed the screening properties of the CDI. We did not find any significant differences between the performances of the BDI and CDI scales, as both scales had AUC levels above 0.90. We also compared the BDI and HADS-D, and found that both the BDI and HADS-D can be used to screen for depression in dialysis patients.

**Conclusion:** The BDI, CDI and HADS had acceptable psychometric properties that can be used as screening instruments for depression, while the HADS-A can be used for anxiety screening in dialysis patients. However, since the HADS has fewer items than the BDI, which

we found to be appropriate for screening for both anxiety and depression, this scale may be preferred to the BDI in a clinical dialysis setting.

#### **5.2.4. Association between depressive/anxiety disorders and perceived HRQOL in dialysis patients**

First, we studied the relationship between psychiatric comorbidity and HRQOL (paper I).

Psychiatric comorbidity was defined as the presence of any anxiety disorder and/or depressive disorder.

Patients with psychiatric comorbidity reported a reduced HRQOL (111) compared to those without comorbidities, and scores on seven out of eight subscales were worse in patients with psychiatric comorbidity. As expected, the MCS, though not the PCS, was more impaired in patients with psychiatric comorbidity. These results were difficult to compare with other studies because other studies have assessed the relationship between depression only and/or anxiety only and HRQOL.

Second, we explored the relationship between HRQOL and depressive disorder and anxiety disorder alone and comorbid depressive and anxiety diagnosis (DA) (paper III). Patients with DA had more impairment on HRQOL than patients with anxiety or depression alone. The finding may suggest that anxiety disorder contributed to strengthening the negative association between depressive disorder and HRQOL in dialysis patients, thus emphasizing the need to diagnose anxiety disorders in patients with depression.

We may speculate what mechanisms may lead to reduced quality of life among patients with a co-occurring anxiety and depressive disorder (DA). Patients with DA may have reduced capacity to cope with dialysis compared to those being merely depressive or anxious.

Furthermore, patients with DA may also be characterized by additional personality traits (eg

neuroticism) or personality disorders to a higher degree than those with only one disorder. Such personality factors may also contribute to HRQOL impairment in these patients. Patients with at least one anxiety disorder showed no significant HRQOL impairment compared to those without any psychiatric disorder. This is in contrast with the previous findings of Cukor et al. (11), who reported significantly lower HRQOL scores in dialysis patients with an anxiety disorder. One possible explanation for the discrepancy in the results between the studies may be that in contrast to the study by Cukor et al., we excluded anxiety patients with comorbid depressive disorders from the statistical analyses on the associations between anxiety disorders and HRQOL.

Reduced HRQOL scores have predicted mortality (127) in dialysis patients. Since depression and anxiety are modifiable risk factors for HRQOL, and because effective treatment for depression and anxiety is available (128), there is of particular interest that cognitive behaviour therapy as well as pharmacological treatment (sertraline) have been associated with improvement of both depression and HRQOL (108, 129). Further clinical trials are needed to identify long terms effect of such treatment and their effects on morbidity and mortality.

Depression and anxiety disorder may exist before HRQOL impairment, thus contributing to HRQOL impairment over time, as well as impaired HRQOL may lead to depression and/or anxiety. Because the present study had a cross-sectional design, we could not determine causal or temporal relationships between anxiety, depression and HRQOL.

In conclusion, suffering from a depressive disorder alone or in particular with comorbid anxiety disorder contributed significantly to an impaired HRQOL. This emphasizes the great importance of identifying both depressive disorders and anxiety disorders in dialysis patients.

#### **5.2.5. Associations between depression/anxiety disorders and mortality in dialysis patients**

Neither depressive nor anxiety disorders as assessed with SCID-I were significantly associated with mortality in the present study. Patients with at least one depressive disorder or at least one major anxiety disorder did not have a significantly higher mortality rate compared with patients without depressive/anxiety diagnoses in both non-adjusted and adjusted (somatic comorbidity, dialysis duration, gender and age) analyses.

Our results differed from those of two previous studies with diagnostic assessments (130, 131). One study reported a significant positive association between physician-diagnosed depression registered from medical charts and mortality. Another study in male American dialysis patients (39) found a significant association between depressive disorders (SCID-I) and poor outcome. Poor outcome was defined in terms of hospitalization and/or death that were merged into one variable. Therefore, we do not know if depression alone was associated with mortality.

One study on predominantly African American dialysis patients (40) showed an association between depression and mortality when using multiple measurements of depression, but failed to show a significant association between depressive affects at baseline and mortality. The authors emphasized that the impact of chronic depression could be a risk factor for death in dialysis patients (40).

A recent study (132) revealed a significant association between high levels of depressive affect assessed with BDI and mortality in ESRD patients observed up to five years. This study showed that the effect of baseline depression did not begin to express itself in mortality rates before nearly two years post-assessment, concluding that this pattern seems to support the predictive nature of depression on mortality. However, because the study did not include

multiple assessments we do not know if chronicity, timespan or both were crucial factors for this positive association. Unfortunately, we do not know the chronicity of depression in our study, as we did not assess depression after baseline and we did not assess the duration of depressive disorders. Furthermore, the short observation period of up to three years, as well as the rather few patients in our study, may explain the lack of association between the presence of depressive disorders and mortality.

Although most studies have reported a positive association between severity of depressive symptoms and mortality across assessment methods (HADS, BDI, CES-D) (82, 83), others have failed to do so (133, 134).

The relationship between depression and mortality is complex. Katon (135) suggested that a model that interacts at three levels has a possible association between depression and mortality in the medically ill. At the first level, depression may contribute to an exacerbation of ESRD through inflammatory pathways. At the second level, the reduced well-being associated with dialysis may lead to depression, hence strengthening the effect of ESRD on HRQOL, function and the self-perceived burden of disease. At the third level, depression is associated with mortality through a non-adherence to treatment (132), a change in immune function (120, 121) and poor nutrition (80).

There is some evidence that high levels of CRP in depressed patients may predict cardiovascular death (136) in ESRD patients. Our depressed patients had high levels of CRP, while more than 50% died from cardiovascular diseases. Even so, when we analyzed the cardiovascular deaths in our patients, we did not find any significant differences between those with and without depression. This may explain why depression was not related to mortality in our study.

Furthermore, patients with comorbid depression and anxiety diagnoses (DA) did not have a significantly higher mortality compared with patients without depressive/anxiety diagnoses.

## 6. General conclusions

- Anxiety and depression were common in dialysis patients. Twenty-two percent of the patients suffered from depressive disorders, 17% of the patients had at least one current anxiety disorder and 8% of the patients suffered from comorbid depressive and anxiety disorder.
- The prevalence of somatoform disorder in dialysis patients was low (1%).
- The HADS-D and BDI performed acceptably as screening instruments for depression, and the HADS-A performed well as a screening instrument for anxiety. Thus, we suggest the following optimal cut-off values for dialysis patients: HADS-A  $\geq 6$  for anxiety, HADS-D  $\geq 7$ , HADS T  $\geq 14$ , CDI  $\geq 12$  and BDI  $\geq 17$  for depression.
- The presence of high levels of CRP  $\geq 6$  mmol/L and low levels of BMI  $\leq 21$  kg/m<sup>2</sup> were associated with psychiatric comorbidity.
- Dialysis patients with depressive disorder reported impaired HRQOL, while those with anxiety disorder did not.
- Patients with comorbid depression and anxiety reported the most serious HRQOL impairment.
- Neither depressive nor anxiety disorders contributed to a compromised survival in dialysis patients.



## **7. Clinical implications**

A high prevalence of psychiatric disorders, i.e. anxiety and depressive disorders and their consequences for HRQOL in dialysis patients, should be of great concern to those who treat these patients. The results of this study show that it is important to identify depressive and anxiety disorders, and in patients with depression, anxiety disorders should also be assessed as the occurrence of both disorders is associated with a significantly poor HRQOL.

We suggest that HADS could be implemented for a screening of depression and anxiety, and those who score above the suggested cut-off scores should be evaluated for psychiatric distress and disorders and a need for treatment.

## **8. Suggestions for future research**

Because of the increase in the proportion of older individuals, improved survival, improved management of dialysis and better pharmacological treatment, the number of dialysis patients is expected to increase over the next few years. This justifies further research in this patient group, in addition to suggestions for future research based on this thesis:

- A long-term follow up study should be conducted in order to find out more about the long-term impact of depression and anxiety in dialysis patients and diagnostic stability of depressive and anxiety disorders.
- Further treatment studies of depression/anxiety should be performed, and their effectiveness for symptom reduction and HRQOL improvement should be assessed.

- The etiology of depression is not known, so there are few studies that support a stress and inflammation hypothesis in depression in the general population. It would be interesting to further study the relationship between stress, inflammation and depression in dialysis patients.
- Further study of comorbid depression and anxiety, as well as their associations with the HRQOL of dialysis patients, is needed.
- Further research is needed to assess the performance of the HADS as a screening instrument for comorbid anxiety and depression in order to help identify patients at a particular risk of an impaired HRQOL.
- Controlled clinical studies to assess coping style, social support and physical training as effective interventions for depression and anxiety are needed.

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