Assessment of the malnutrition-inflammation complex syndrome and its association with depression and mortality in patients after kidney transplantation

Doctoral thesis

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INTRODUCTION

In the last decades along with the development of the medical science the life expectancy at birth has increased substantially, resulting in the continuous aging of the population. Due to new and effective therapeutic methods, the life expectancy of patients suffering from certain chronic diseases has been elongated with years, or sometimes decades. Similarly to other chronic diseases the prevalence of end stage renal disease (ESRD) also continuously increases. Similarly to the general population the average age of the patients has also increased. Although there are different treatment methods for chronic kidney disease (CKD), in most cases there is no definitive cure. With the available methods the pace of the progression can be decreased in the early stages, or in case of ESRD renal replacement therapy can be introduced.

In spite of the substantial technical development of the last few decades, mortality of ESRD patients, especially of patients on maintenance dialysis is still high. Quality of life of patients is exceptionally low, even compared to other chronic disease populations. Similarly to the general population, cardiovascular diseases account for the highest percentage of mortality. As the number of ESRD patients increases and the treatment costs make up for a significant portion of the overall healthcare budget, there is an urgent need to explore factors leading to the negative outcome and to evolve successful treatment strategies.

Among the possible causes that could account for the higher mortality and hospitalization rate, chronic inflammatory state and protein-energy malnutrition (PEM) are at the beginning of the list. Epidemiological studies found conclusively strong association between the negative outcome and malnutrition and markers of inflammation. Additionally, several factors that cause the one, can as well lead to the other. Immune mechanisms change in the body of malnourished, cahectic patients, and thus the inflammation which once started with the aim of protection, becomes chronic.

During inflammation several mechanisms can cause the loss of appetite. In the ab ovo malnourished patients the long term, often clinically undetectable micro-inflammatory state further increases the need for nutrients and calorie that leads to further weight loss, especially the loss of muscle and in severe cases results in cachexia. Due to this close association between inflammation and malnutrition this state is called *malnutrition-inflammation complex syndrome* (MICS), or *malnutrition-inflammation cachexia syndrome*, although the terms protein-energy malnutrition (PEM) or protein-energy wasting (PEW) are also often used as synonyms.

There were several attempts to measure MICS as a complex, multifactorial entity, but it has bee made clear that this state is much more complex than being characterized by a single clinical or laboratory parameter. To offset difficulties related to the measurement of MICS in clinical practice, Kalantar-Zadeh et al. recently developed and validated among patients on hemodialysis a semi-quantitative scoring system, the *Malnutrition-Inflammation Score* (MIS, *Kalantar-score*). This score showed independent association with nutritional and inflammatory markers, anemia, and predicted hospitalization and mortality among patients on dialysis.

Although the MICS has been described primarily in patients on maintenance dialysis, several factors can lead to its development also in patients after kidney transplantation: the immune reaction of the host to the presence of the transplanted allograft, continuous administration of immunosuppressive drugs, rejection episodes, or even the decreased kidney function can all potentially play a role in the development and maintenance of the condition.

The mechanisms that start during MICS in a well functioning organism are primarily aimed to attenuate inflammation. These mechanisms play a major role in the development of the so called *„sickness behavior"* with fatigue, increased need for sleep and loss of appetite. The overlap between these symptoms and the symptoms of mood disorders is so evident that some authors consider depression being the part of the malnutrition-inflammation complex syndrome.

Depressive symptoms and anxiety disorders are the most frequent psychological problems in patients on dialysis and also in patients after kidney transplantation. Several lines of evidence suggest that there is a complex, two-dimensional relationship between depressive symptoms and inflammatory state. Studies from both the general population and CKD patients suggest that inflammatory cytokines can cause depressive symptoms and levels of inflammatory markers are increased in the blood of depressed patients. As one of the most frequent symptoms of depression is the loss of appetite, and energy-consumption is increased during inflammatory state, a complex, multidimensional association can be postulated between malnutrition, inflammation and depression. To our knowledge this association has not been examined previously in patients after renal transplantation.

The MICS is associated with negative clinical outcome among CKD patients, and it is an independent cardiovascular risk factor. Among others, possible consequences of MICS in ESRD patients are oxidative stress, erythropoietin resistance, and higher morbidity and mortality rate. Studies carried out among patients on hemodialysis found the MIS score to be

an independent predictor of mortality. However, there are no published data about this relationship from kidney transplanted population.

AIMS

Adaptation of the malnutrition-inflammation scale to patients after kidney transplantation

The malnutrition-inflammation scale has not been used before in patients living with a renal allograft. However, extensive clinical usage in this special patient population needs to be preceded by a detailed examination, whether this scale reliably measures the nutritional and inflammatory state of the patients.

Our aims were to examine if:

- The MIS score shows association with objective markers of the nutritional and inflammatory state, as abdominal circumference, serum pre-albumin and leptin level, C-reactive protein level (CRP), interleukine-6 (IL-6) and tumor necrosis factor-α (TNF-α) concentration;
- Additionally we examine with the help of structural equation modeling (SEM) whether the MIS is a more informative measure of the complex phenomenon of MICS than the individual markers of inflammatory and nutritional state.

Association between the malnutrition-inflammation syndrome and depressive symptoms in patients with renal transplant

Several lines of evidence indicate a complex relationship between depression and nutritional and inflammatory state. This assumption has previously been examined several times in patients on dialysis, where the malnutrition-inflammation score was associated to the severity of depression. To date there has not been such survey performed among kidney transplanted patients.

Our current study aimed to examine:

- Whether the depressive symptoms are in association with individual markers of nutrition and inflammation, as albumin and pre-albumin levels, CRP and IL-6 concentration and the MIS score;
- Whether the MIS score is in a relationship with depressive symptoms independently from important clinical and socio-demographic variables in patients after kidney transplantation.

ASSOCIATION BETWEEN THE MALNUTRITION-INFLAMMATION SYNDROME AND MORTALITY IN PATIENTS AFTER KIDNEY TRANSPLANTATION

After confirming that the MIS is a useful tool to assess the severity of PEM also in patients with renal transplant, we aimed to examine in prospective setting the association between the MICS characterized by the MIS and the negative clinical outcome (mortality and return to dialysis) in a cohort sample of renal transplant recipients.

The aims of our study were to assess:

- Whether the MIS used for the characterization of the MICS prospectively predicts mortality independently from other co-variables;
- And whether the MIS prospectively predicts return to dialysis independently from other co-variables.

METHODS

PATIENTS AND DATA COLLECTION

The thesis is based on the cross-sectional cohort study performed at the Department of Transplantation and Surgery at the Semmelweis University, Budapest between February and August 2007 *(Malnutrition-Inflammation in Transplant – Hungary Study (MINIT-HU Study))*. All prevalent kidney transplant recipients 18 years of age or older (n=1214) who were followed at this transplant outpatient clinic on December 31, 2007, were invited to participate in this observational study. Exclusion criteria were: acute rejection within the last 4 weeks, current hospitalization, transplantation in the previous 3 months, acute infection or bleeding. The patients were approached by members of our work group (PhD students including myself, medical student researchers, and a trained assistant) during waiting for their regular nephrological control.

Socio-demographic and life-style related data (age, gender, education, employment status, marital status, financial status, smoking status, etc.) together with details of medical history (etiology of chronic kidney disease (CKD), transplantation-related data medication, co-morbidities, menopause status etc.) were collected at enrollment. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula. The malnutrition-inflammation score was obtained during a short interview. I coordinated data collection and data entry, and the MIS scale was obtained in most of the cases by me.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Semmelweis University (49/2006). Before enrollment, patients received detailed written and verbal information regarding the aims and protocol of the study and gave written consent to participate.

ASSESSMENT OF THE MALNUTRITION-INFLAMMATION SYNDROME

To assess the malnutrition-inflammation syndrome we used the malnutrition-inflammation score (MIS) developed and published by Kalantar-Zadeh et al. The MIS has 10 components, each with four levels of severity, from 0 (normal) to 3 (severely abnormal). The sum of all 10 MIS components ranges from 0 (normal) to 30 (severely malnourished); a higher score reflects a more severe degree of malnutrition and inflammation status. Co-morbidity was scored the following way: 0 if no medical illnesses were present except CKD; 1, mild co-morbidity, excluding such major co-morbid conditions (MCCs) as severe congestive heart failure, severe coronary artery diseases, clinically evident acquired immunodeficiency syndrome (AIDS), moderate to severe chronic obstructive pulmonary disease, and metastatic malignancies; score 2, moderate co-morbidity (including one of the diseases listed under MCCs); and score 3, two or more MCCs. The assessment of the nutritional state was performed according to the conventional Subjective Global Assessment (SGA) guidelines

ASSESSMENT OF DEPRESSIVE SYMPTOMS

To assess the severity of depressive symptoms, all patients completed the Center for Epidemiologic Studies-Depression (CES-D) scale. In case the patient was unable to complete the questionnaire (e.g. illiterate or severely disabled patient) a member of the work group provided assistance. The possible score on the CES-D scale ranges between 0 and 60 points; higher scores indicate more depressive symptoms. To determine the risk of clinically relevant depression we used a cut-off value of 18 points as suggested by Hedayati et al. for patients with CKD. Patients with CES-D$\geq$18 are referred to as “high risk for depression” or “depressed” while patients with CES-D<18 are called “low risk for depression” or “non-depressed”. The Hungarian version of the CES-D scale has been prepared according to a recommended procedure and has been validated by our work group in Hungarian hemodialysis and kidney transplant recipients.

LABORATORY PARAMETERS

Laboratory data were extracted from the charts and from the electronic laboratory database of the hospital. The following laboratory parameters were tabulated: hemoglobin (Hb), serum C-reactive protein (CRP), total cholesterol, triglyceride, ferritin, transferrin, albumin, pre-albumin, creatinine and blood urea nitrogen.

Additional blood specimens were obtained at the same time, centrifuged, and serum samples were stored at -70 C^o until future use. From these samples high sensitivity interleukine-6 (IL-6), tumor necrosis factor-α (TNF-α) and leptin levels were measured using immunoassay kits based on solid-phase sandwich enzyme linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN).

CO-MORBIDITIES

We used the modified Charlson Comorbidity Index, which is a weighted scoring system based on the presence or absence of each of 17 variables. Earlier it has been reported that the CCI was a predictor of survival in kidney transplanted patients. Since one of the variables is the presence of moderate to severe renal disease, in patients with ESRD scores range from two to a possible maximum of 33.

TRANSPLANTATION RELATED DATA AND DONOR CHARACTERISTICS

The following transplantation related data were extracted from the medical records: current medications, time elapsed since the time of the transplantation, previous time on dialysis, type of transplantation (deceased or living related), history of acute rejection, HLA mismatch, panel reactive antibodies titer (PRA), cold ischemic time (CIT), donor age and gender and history of delayed graft function.

FOLLOW-UP

Annual follow-up visits were scheduled for all patients, when all the laboratory data mentioned above and data about current immunosuppressive and other medications were updated, and MIS, body weight, height and other anthropometric variables were reassessed. By the end of 2009 still-enrolled patients have completed 3 follow-up visits. Patients were followed for 31 months (median, [IQR]: 31.3, [3.3] months). The primary outcome variable was all-cause mortality with functioning graft and death-censored graft loss (return to maintenance dialysis). Deaths and re-initiations of maintenance dialysis were ascertained from the hospital database, and those events were registered that occurred first.

STATISTICAL ANALYSES

The data were summarized using proportions, means (±standard deviation, SD) or medians (interquartile range, IQR) as appropriate. Categorical variables were analyzed with the chi-square test, while continuous variables were compared using Student's t-test or ANOVA test, the Mann-Whitney U test or Kruskal-Wallis H test as appropriate. Association between the MIS score or the CES-D score versus continuous variables was assessed by using Spearman or partial correlation analysis. In all statistics, two-sided tests were used and the results were considered statistically significant if $\alpha \leq 0.05$.

Structural equation modeling (SEM) was used to test goodness of fit of one and two factor models describing the relationship of abdominal circumference, leptin, pre-albumin, CRP, IL-6 and TNF-α with MIS. For this analysis we transformed TNF-α and leptin values in order to make variances comparable to the variances of other variables.

We used linear regression analysis to assess independent associations between the CES-D score and variables reflecting inflammation. To obtain normally distributed data the CES-D score was square-root-transformed and the transformed variable was used as a dependent variable in the multivariate linear regression model. The model was built using known socio-demographic correlates of depression (age, gender, education, marital status, employment status, self-reported financial status) and the most important kidney disease related variables (eGFR, Charlson Comorbidity Index) that have been shown to be associated with depressive symptoms, in addition to inflammatory and nutritional markers (CRP, IL-6, pre-albumin and the MIS score). The MIS scale includes BMI, serum albumin and transferrin levels, therefore these variables were not entered in the model separately.

The association of MIS with the two outcomes (death and return to dialysis) was assessed by means of semiparametric competing-risks regression analyses. We also assessed this association using time-dependent data as sensitivity analysis. The association between the MIS and mortality was assessed using time-dependent Cox regression analysis and Kaplan-Meier plots. The variables entered in the multivariable-adjusted models were selected by theoretical considerations; we included predictors in the models which were known to be associated with graft loss or mortality based on external evidence and clinical experience, and which were available in our database. Age, gender, CCI, systolic blood pressure, transplant vintage, history of delayed graft function, smoking status, type of donor, history of acute rejection, total time on dialysis and number of HLA-mismatches were entered as baseline data. The MIS, estimated GFR and hemoglobin were entered as time-dependent variables.

MIS was analyzed both as a categorical variable and as a continuous variable (categorized according to the median of MIS; ≤3 vs >3). There was no missing data at the baseline data collection, and less than 1% of the data lost during the follow-up. In time-dependent analyses missing data points were replaced using the last value carried forward method.

Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, USA) and STATA version 10.1 (STATA Corporation College Station TX) software packages.

RESULTS

PRESENTATION OF THE STUDY SAMPLE

From the 1214 patients meeting the eligibility criteria 205 (17%) refused to participate in the study and 16 patients (1%) were excluded based on exclusion criteria. Therefore the studied sample consisted of 993 subjects.

There were less men among those who refused to participate (57% vs. 67%; $p<0.01$), but there was no significant difference in age between the two groups (51±13 vs. 52±13 years, p=NS). Among the enrolled subjects 57% were men, the average age was 51 ± 13 years, the prevalence of diabetes was 21%. The median (IQR) of time elapsed since transplantation was 71 (75) months. The estimated GFR was 51±21 ml/min/1.73m^2, which corresponds to third stage renal disease. Two groups were formed based on median MIS score, and we examined whether the groups differ regarding the studied parameters. In the group with above median MIS score there were less men, the mean age was higher, and the time since transplantation was significantly longer. Patients with below median MIS score had a better kidney function, less comorbidities, and higher level of hemoglobin. Thus, generally, subjects with higher MIS score were elder and had a worse health condition than those with lower MIS score.

PREVALENCE OF MALNUTRITION-INFLAMMATION SYNDROME AND ITS CORRELATES IN PATIENTS AFTER KIDNEY TRANSPLANTATION

The two groups formed by the median MIS score significantly differed in all inflammatory and nutritional parameters except for blood lipid and leptin concentrations. This suggests that the high and low MIS scores indeed separate participants into two distinctive groups with different nutritional and inflammatory states.

In correlation analyses we investigated the relationship of nutritional and inflammatory parameters with age and renal function. The age had a significant moderate positive correlation with abdominal circumference ($R=0.299$; $p<0.001$) and IL-6 (rho=0.247;

p<0.001), weak but significant positive correlation with CRP and leptin (rho=0.146 and 0.092, respectively; p<0.01), and very weak, negative correlation with pre-albumin level (R=-0.068; p<0.05), while TNF-α showed no association with age. Estimated GFR negatively correlated with IL-6 (rho=-0.156), TNF-α (rho=-0.220), CRP (rho=-0.089), pre-albumin (R=-0.263) and leptin (rho=-0.159; p<0.01 everywhere). Based on our results most of the nutritional and inflammatory parameters showed the expected association with age and kidney function.

The MIS score significantly correlated with age (rho=0.213), estimated GFR (rho=-0.281), time since transplantation (rho=0.177), and hemoglobin level (rho=-0.315). CRP and inflammatory cytokines (IL-6, TNF-α) also showed significant positive correlation with MIS (rho=0.094 vs. 0.231; p<0.01). Additionally, we found negative association with nutritional parameters (body weight (-0.254), abdominal circumference (-0.144), pre-albumin level (-0.165), leptin level (-0.057)). These associations remained significant even after adjustment for age, gender and kidney function.

The adjusted correlation between the total score and the individual items of the MIS scale was the highest for the question about appetite (rho=0.343) and for the items of the SGA related to the nutritional status (decreased fat stores (rho=0.444), signs of muscle loss (rho=0.439)). These results suggest that these relatively subjective items were in the closest relationship with the total score.

To more precisely evaluate the complex associations in our data we used Structural Equation Modeling (SEM). The aim of this analysis was to examine, whether the MIS score incorporates the characteristics of both the nutritional and the inflammatory state of the patients. We analyzed our models in two ways: assuming one and two („inflammation” and „malnutrition”) latent variables.

We included every relevant inflammatory and nutritional variables (leptin level, abdominal circumference, pre-albumin level, CRP, IL-6, TNF-α) in the model, and we examined, how does this model fit to our data. The goodness of fit statistics showed a better model fit in case of the two latent variables. The correlation between the „nutrition” latent variable and the MIS score was -0.38 and the co-variance significantly differed from zero (-2.92; p<0.001). Similarly, the correlation between the „inflammation” latent variable and the MIS score was 0.32 and the covariance 1.49 (p<0.001). According to these results the MIS reflects the characteristics of both the inflammation and the nutrition latent variables.

Twenty out of the 993 participants did not complete CES-D questionnaire, therefore in this study we analyzed the data of 973 patients.

One-fourth (25%) of the patients had a high risk for depression (CES-D score≥18). In the high risk group there were significantly more women (53% vs. 39%), smaller number of patients were married or lived with a partner (56.4% vs. 69.8%), fewer patients had higher education (47.9% vs. 58.3%), significantly more patients had financial difficulties (67.5% vs 41.2%), and fewer patients had a full or part-time job (17.4% vs. 30.8%). Hemoglobin level and estimated GFR were significantly lower for the depressed patients. Serum IL-6 concentration was higher in the depressed group, but there was no difference between the two groups in the levels of TNF-α, albumin, pre-albumin and CRP. The percentage of depressed patients was the highest in the upper tertile of MIS score, and lowest in the lower tertile (14.5%, 27.5% and 36.6% in the lower, middle and upper tertile, respectively; linear-by-linear association; $p<0.001$).

To assess the association between measures of nutrition, inflammation, clinical and laboratory characteristics versus the CES-D score, partial correlation analyses, corrected for age, sex and eGFR were performed. We found weak but significant positive correlation between the CES-D score vs. IL-6 and the Charlson Comorbidity Index (rho=0.124 and 0.103, respectively; $p<0.01$ for both). The CES-D score had the strongest correlation with the MIS score (0.262; $p<0.001$).

To assess if the association between the CES-D score and the MIS is independent of the socio-demographic, clinical and laboratory parameters assessed, a multivariable linear regression model was constructed, based on theoretical considerations. The distribution of the CES-D score was skewed therefore the square root transformed CES-D score was used as dependent variable in the multivariate regression model.

We included those variables in the multivariable adjusted model that showed a significant association with CES-D score in univariate analyses and/or are associated with the higher prevalence of depression or depressive symptoms according to the literature. The final model included age, gender, education, marital status, employment status, self-reported financial status, eGFR, CRP, IL-6, pre-albumin, Charlson Comorbidity Index, and MIS ($r^2=0.176$). In this model older age (B=0.009; p=0.01), female gender (B=0.257; p=0.005), worse financial status (B=0.577; $p<0.001$), single, divorced or widow(er) status (B=0.322; $p<0.001$), pre-albumin level (B=0.013; p=0.04), and higher MIS score (B=0.109; $p<0.001$) remained in a

significant relationship with the CES-D score independently from the other variables. The association between education and depressive symptoms failed to reach statistical significance (B=0.158; p=0.07). The CES-D score was in an independent relationship with the MIS score, and this association was stronger and more robust than its relationship with any other nutritional or inflammatory marker.

RELATIONSHIP BETWEEN MALNUTRITION-INFLAMMATION SYNDROME AND MORTALITY IN PROSPECTIVE SETTING

During the 31 months follow-up period 64 patients died and 74 returned to maintenance dialysis. Both events occurred less frequently among patients with low baseline MIS score (MIS≤3) compared to the high MIS (MIS>3) group (crude mortality rate: 13/1000 vs. 48/1000 patient year; p<0.001; crude graft loss rate: 12/1000 vs. 59/1000 patient year; p<0.001).

One point increase in the baseline MIS score showed association with negative outcome both in univariate analyses (HR mortality = 1.252 [95% CI: 1.191-1.315]; HR graft failure = 1.254 [95% CI: 1.196-1.315]), and also in multivariate analyses (HR mortality = 1.130 [95% CI: 1.056-1.209]; HR graft failure = 1.189 [95% CI: 1.095-1.291]) adjusted for age, gender, estimated GFR, Charlson co-morbidity score, average systolic blood pressure, time elapsed since transplantation, history of delayed graft function, CRP-level, hemoglobin-level and smoking status.

Similarly, being in the group with higher than median MIS score (MIS>3) was also associated with negative outcome in crude, uncorrected analyses (HR mortality = 4.485 [95% CI: 2.517-7.991]; HR graft failure = 5.490 [95% CI: 3.120-9.662]), and in multivariate analyses corrected for the aforementioned variables (HR mortality = 1.818 [95% CI: 1.002-3.297]; HR graft failure = 2.606 [95% CI: 1.369-4.963]).

We found similar results in Cox regression analysis when we included only the baseline MIS score in the model, and also when we used the MIS score as time-dependent variable.

In our sample a patient with a higher MIS score had a higher chance for one of the negative outcomes (death or return to dialysis) during the follow-up period independently from other clinical or laboratory variables. Our results suggest that the higher malnutrition-inflammation score independently predicts higher risk of mortality and graft failure in patients with renal transplant.

CONCLUSIONS, NEW FINDINGS

In our survey we assessed the severity of the malnutrition-inflammation syndrome with the help of the malnutrition-inflammation score, and examined its relationship with depressive symptoms and clinical outcome among patient after kidney transplantation. Here I summarize our new results:

- We showed for the first time that the malnutrition-inflammation score showed association with objective markers of the nutritional and inflammatory state in patients after kidney transplantation;
- We found the MIS a more informative measure of the complex phenomenon of MICS than the individual markers of inflammatory and nutritional state;
- Depressive symptoms were in association with markers of nutrition and inflammation including the MIS score in patients living with a kidney allograft;
- The MIS score was in a relationship with depressive symptoms independently from important clinical and socio-demographic variables;
- The MIS prospectively predicted mortality independently from other important clinical and laboratory co-variables;
- The MIS prospectively predicted return to dialysis independently from other clinical or laboratory measures.

In summary we showed that the malnutrition-inflammation score is a useful tool also in patients after kidney transplantation, and gives reliable information about the malnutrition-inflammation complex syndrome. This easy-to-use, low-cost instrument could be used for risk assessment in epidemiologic studies of large sample sizes, and also in everyday clinical practice to assess nutritional and inflammatory state of the patients.

Among patients on dialysis depressive symptoms show association with the nutritional and inflammatory state of the patients. In our study the MIS score was in relationship with depressive symptoms that frequently occur also in patients after renal transplantation, and this relationship was independent from important socio-demographic and clinical covariables. Further studies are needed to explore the complicated network formed by the presumed pathophysiological mechanisms behind this relationship. Additional intervention studies are required to examine whether the treatment of depression could improve the nutritional and inflammatory state of the patients. Finally, to explore if MICS affected the efficacy of antidepressant therapy would entail substantial clinical advantage.

Despite all therapeutic efforts the cardiovascular mortality of chronic kidney disease patients is still high; therefore there is an urgent need to explore alternative risk factors. Malnutrition-inflammation syndrome showed association with mortality in patients on dialysis. In our prospective observational study we identified the MICS as a risk factor, and we showed that worse nutritional and inflammatory state characterized by higher MIS score was in independent relationship with higher risk of mortality and graft failure. This simple instrument could be an important tool in estimating risk in clinical practice. However, further studies are needed to determine whether mortality risk could be decreased with the improvement of the nutritional an inflammatory state in this patient population.

PUBLICATIONS

Publications associated with the thesis

Publications in international journals:

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