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FACTORS AFFECTING THE OUTCOMES OF CHRONIC RENAL FAILURE IN HEMODIALYSIS

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Abstract

Relevance. High mortality in dialysis patients (6.3–8.2 times higher than in the general population) motivate to search and identify potential risk factors to improve survival.

Aim. This review is devoted to the analysis of the literature on the identification of factors affecting outcomes in patients with chronic renal failure who are on hemodialysis.

Search strategy. Search of scientific publications in the search engines Pub Med, Google Scholar, Google Academia, in the electronic scientific library eLibrary.ru, CyberLeninka 10 years deep. Criteria for search information: years of search included one decade (2009-2019); publications were in Russian, Kazakh and English; full-textured epidemiological and clinical studies. Exclusion criteria: publications with animal studies, recurring publications, conference proceedings, and clinical cases.

Results. As the main predictors of mortality and survival of patients on hemodialysis, according to the literature, the dose and frequency of dialysis, residual renal function were studied.

Conclusion. Analysis of the literature data showed that the most significant factor determining the outcomes of chronic renal failure in hemodialysis is residual renal function.

Key words: *chronic renal failure, hemodialysis, mortality, survival.*

Резюме

ФАКТОРЫ, ВЛИЯЮЩИЕ НА ИСХОДЫ ХРОНИЧЕСКОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТИ ПРИ ГЕМОДИАЛИЗЕ

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Резюме

Актуальность. Высокая смертность у диализных пациентов (в 6,3-8,2 раза выше, чем в общей популяции) мотивирует на поиск и выявление потенциальных факторов риска, чтобы улучшить выживаемость.

Цель. Данный обзор посвящен анализу литературных источников по выявлению факторов, влияющих на исходы у пациентов с хронической почечной недостаточностью, находящихся на гемодиализе.

Стратегия поиска. Проведен поиск научных публикаций в поисковых системах Pub Med, Google Scholar, Google Academia, в электронной научной библиотеке eLibrary.ru, CyberLeninka глубиной 10 лет. Критерии включения: глубина поиска составила 10 лет (2009-2019); публикации на казахском, русском и английском языках; полнотекстовые эпидемиологические и клинические исследования. Критерии исключения: публикации с исследованиями, проведенными на животных, повторно встречающиеся публикации, материалы конференций и клинические случаи.

Результаты. В качестве основных предикторов смертности и выживаемости пациентов, находящихся на гемодиализе, по данным литературы, изучались доза и частота проведения диализа, остаточная функция почек.

Выводы. Анализ литературных данных показал, что наиболее значимым фактором, определяющим исходы хронической почечной недостаточности при гемодиализе, является остаточная функция почек.

Ключевые слова: *хроническая почечная недостаточность, гемодиализ, смертность, выживаемость.*

Түйіндеме

СОЗЫЛМАЛЫ БҮЙРЕК ЖЕТІСПЕУШІЛІГІМЕН АУЫРАТЫН НАУҚАСТАРДАҒЫ ГЕМОДИАЛИЗ КЕЗІНДЕГІ АЯҚТАЛУЛАРҒА ӘСЕР ЕТЕТІН ФАКТОРЛАР

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Өзектілігі. Диализ кезіндегі жоғары деңгейдегі өлім көрсеткіші (жалпы популяцияға қарағанда 6,3-8,2 есеге артық) маңызды қауіп факторларына іздеуге ыңдаландырады. Осы шолу әдеби мәліметтерді сараптау арқылы созылмалы бүйрек жетіспеушілігімен ауыратын науқастардағы гемодиализ кезіндегі аяқталуларға әсер ететін факторларын анықтауға бағытталған.

Іздеу стратегиясы. Ғылыми басылымдарды іздеу Pub Med, Google Scholar, Google Academia, eLibrary.ru, CyberLeninka іздеу системалары арқылы жүргізілді. Тереңдігі 10 жыл. Қосу критерийлері: іздеу тереңдігі 10 жыл (2009-2019); қазақ, орыс және ағылшын тілдеріндегі басылымдар; толық мәтінді эпидемиологиялық және клиникалық зерттеулер. Шығару критерийлері: жануарлар туралы мақалалар, қайталанатын жарияланымдар, конференция материалдары, клиникалық жағдайлар.

Нәтижесі. Әдеби мәліметтерге сүйенсек, гемодиализдегі науқастардың өлім және аман қалу предикторлері болып гемодиализдің дозасы, реттілігі және қалдық бүйрек функциясы саналады.

Қортынды. Алайда, созылмалы бүйрек жетіспеушілігімен ауыратын науқастардағы гемодиализ кезіндегі аяқталуларға әсер ететін ең маңызды факторы ретінде қалдық бүйрек функциясы қарастырылады.

Негізгі сөздер: созылмалы бүйрек жетіспеушілігі, гемодиализ, өлім, аман қалу.

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Relevance

Nowadays it is approved to take into account the classifications of chronic kidney disease (CKD) instead of traditional classifications of chronic renal failure (CRF) in estimating the function of kidney. Special feature of this classification is determining the five stages of development of kidney disease on the basis of level of glomerular filtration rate (GFR).

Chronic kidney disease (CKD) is comparatively slowly progressing pathology, represented by the presence of kidney injury or functional condition of kidneys. Group of patients who have Chronic Kidney Disease includes all the people with renal injury regardless of level of glomerular filtration rate (GFR), those who glomerular filtration rate less than 60 ml/min/1.73m² during 3 months period or more independently of presence of renal injury; patients with terminal chronic renal failure with glomerular filtration rate lower than 15 ml/min/1.73 m² [10, 29].

It is known that biomarkers of renal injury are: albuminuria, change of urine sediment, signs of renal tubular injury (renal tubular acidosis, Fanconi's syndrome and etc.), modifications detected using histopathological and imaging analysis (polycystosis, kidney displasia, hydronephrosis due to obstruction, increased kidney size because of infiltrative diseases, renal artery stenosis, small hyperechoic kidney), transplanted kidney [3, 21].

The main causes of chronic renal failure in adulthood, according to some researchers, are: diabet (33%), cardiovascular disease (21%) and glomerular lesions (19%) [4].

Approximately 10-11% of general population suffer from chronic kidney diseases [4]. More precisely in USA this number fluctuates between 11,6% and 15,3%; in China and Australia – 14 and 13,4% respectively; in Spain and Japan expansion reaches 21,3% and 20%, respectively. The existence of chronic kidney disease in elderly people have

increased pattern and accounts for number from 23,4% to 35,8%, if they have cardiovascular pathology or diabetes – in 40% cases [3].

However, only 1% of population is diagnosed to have chronic kidney diseases. Annual growth of chronic renal failure patients treated with hemodialysis is 100 to every million population [4]. Frequency of happening new cases of terminal renal failure in USA makes up from 0.13 to 0.15 patients per 100 people[8].

Chronic renal failure (CRF) therapy has two stages: conservative and renal replacement. Conservative stage (front dialysis) is meant to prevent and avoid factors of risks [41]. In renal replacement stage patients are cured with hemodialysis or had their kidneys transplanted [6, 10].

Renal replacement therapy (RRT) is the main method of curing chronic renal failure patients (CRF) [5]. Many understand the notion “renal replacement therapy” as treating with hemodialysis.

Hemodialysis - is the primary method of treating Chronic renal failure, in which through synthetic semipermeable membrane takes place diffusion process of creatinine, urea and electrolytes that accumulated in organism along with uremia [9, 44]. Usually hemodialysis lasts for 4-6 hours with frequency 2-3 times a week.

According to Marchenko D.N. and other authors [5], patient with first symptoms of renal failure of terminal stage need to be treated with dialysis immediately. Uremic pericarditis, encephalopathy, polyneuropathy are the latest symptoms, illustrated by far gone renal failure with irreversible uremic complications.

Unfortunately, during chronic hemodialysis many components of uremia still persists in organism, though their level significantly decreases. Moreover, at a time time of taking hemodialysis therapy 18–39% of inmates are diagnosed encephalopathy, cognitive impairment and dementia, which are in turn leads to high level of mortality or disability [37]. Complications arising during program hemodialysis are: pericarditis, diverticulosis, hepatitis, impotence and kidney cysts. It is also known that renal osteodystrophy progresses or comes out as osteomalacia with bone pain and fractures [7, 29].

Despite the fact that hemodialysis prolongs the life expectancy of patients with terminal renal failure, the mortality is still in high level [1, 32]. According to some authors, death rates caused by all diseases combined are 6.3–8.2 times higher in dialysis patients compared to the general population [16].

The peaks of mortality mostly noticed among the first year dialysis patients. Research from India showed, that 9-13% of people taking programmed dialysis died in their first year therapy. Of these, more than half (63,1%) cases mortality happened in first months[13]. Also, the most frequent cases of death, based on United States Renal Data System (USRDS), happens in 2-4 months period from the start of programmed hemodialysis [2, 39].

With respect to causes of mortality, some authors claim, most common sepsis (36,8%) and coronary heart disease (26,3%) [13]. The results of a study conducted in Novosibirsk (Russia) showed that cardiovascular complications prevailed between of causes of mortality and amounted to 39.5%. It was also revealed that the subjects of death were infectious diseases and malignant neoplasms

26.3% and 7.9%, respectively [1]. Authors of several researches share the same idea, that the leading reason of such a high mortality rate among dialysis patients - is cardiovascular diseases [15, 25].

Another vital outcome in program hemodialysis, along with mortality, goes survival of patients with chronic renal failure. Despite today there are lots of studies about the survival factors in hemodialysis, the authors' opinions are controversial.

The purpose of this review is to analyze the English-language and Russian-language literary sources studying factors, that have an impact on outcome of hemodialysis therapy on chronic renal failure patients.

Search strategy

The search for English-language and Russian-language literary sources was carried out in the abstract data base Pubmed (<https://www.ncbi.nlm.nih.gov>), Google Scholar (<https://scholar.google.ru>), in the electronic scientific library eLibrary.ru (<https://elibrary.ru>), CyberLeninka (<https://cyberleninka.ru>).

We used the following keywords when conducting a search in Russian-language search network: Chronic renal failure, Chronic kidney disease, residual renal function, hemodialysis and survival, hemodialysis and mortality. The keywords that were used when searching for literary sources in English-language search sites were: end-stage renal disease AND hemodialysis, end-stage renal disease, survival, mortality AND hemodialysis, residual kidney function AND end-stage renal disease AND hemodialysis, residual kidney function AND survival AND hemodialysis

Criteria for search information: years of search included one decade (2009-2019); publications were in Russian, Kazakh and English; full-textured epidemiological and clinical studies. *Exclusion criteria:* publications with animal studies, recurring publications, conference proceedings, and clinical cases.

Results

A review of literature revealed that dialysis dose may be considered as one of the survival factors for patients on hemodialysis. *Depner T. et al.* in his showed, that survivability was directly dependent on dose of dialysis (Kt/V), its frequency and and serum albumin. From author's opinion, when increasing the dose, dialysis had greater effect on women rather than on men [17]. But, the results of *Eknoyan G. et al's* study showed no interconnection between survival and the decreased dose of hemodialysis [18].

An important role in the survival of patients with chronic renal failure is played by the frequency of hemodialysis. According to some authors, hemodialysis at least 3 times a week contributes to better patient survival [2, 13]. At the same time, a comparison of patients receiving hemodialysis twice and three times a week did not reveal statistically significant differences in survival in a study among the Chinese population [23]. Nevertheless, the predominant number of studies are devoted to studying the effect of residual renal function, in particular its presence or absence, its effect on the outcomes of chronic kidney disease patients in hemodialysis therapy. [30]. Preservation of residual renal function (urine volume of more than 200 ml / day) favorably affects mortality predictors in dialysis patients, such as hypervolemia [12], left ventricular

hypertrophy (LVH), congestive heart failure [11, 46], heart rhythm disturbance [38] and ischemic strokes [14].

According to *Mathew A.T. et al.* residual renal function is associated with better patient survival, better quality of life with regard to the health of patients on hemodialysis [27]. *Obi Y. et al.* As a result of his studies with the determination of urea clearance as an indicator of residual renal function, it was found that an increase in urea clearance 1 year after the onset of hemodialysis was associated with survival ($p = 0.001$ in all models). So, comparisons of patients with urea clearance from 3.0 to 6.0 ml / min per 1.73 m² with patients in whom this indicator was from 1.5 to 3.0 and 1.5 ml / min per 1.73 m² 1 year after the start of hemodialysis showed that higher mortality was observed among the second group of patients. These differences remained statistically significant even after correction for changes in body mass index and other laboratory parameters 1 year after the start of hemodialysis (HR = 1.26; 95% CI (1.08–1.47) and HR = 1.67; 95% CI (1.44–1.94), respectively).

The authors also studied the effect of urine volume on mortality during hemodialysis. As a result of the study, a significant tendency to a decrease in mortality with a higher urine volume was established ($P_{\text{trend}} = 0.001$ in all models). At the same time, patients with a faster decrease in urine volume showed a higher risk of mortality [30].

Studies in Korea also showed that residual urine volume was a better predictor of mortality compared to other indicators of residual renal function. A prospective cohort study compared the values of residual renal function in 1946 patients on dialysis at 36 dialysis centers in Korea (urea, creatinine clearance, GFR-urea, microglobulin GFRb2 from urine collected per day). According to the Cox proportional risk model, residual urine volume and glomerular filtration rate were associated with mortality, regardless of cause (HR = 0.96 95% CI (0.94-0.98), HR = 0.98; 95% CI (0.95 -0.99), respectively). However, only the urine volume in this model best predicted mortality ($p = 0.01$). Residual urine volume was associated with a lower risk of death and showed a stronger association with survival than other indicators. According to the authors, the determination of the volume of residual urine may be useful for predicting the survival of patients on hemodialysis [22].

A review of literature showed that there are studies in which residual renal function is also considered as a direct factor in the survival of patients on hemodialysis, affecting the function of the left ventricle. It is known that left ventricular hypertrophy (LVH) and systolic dysfunction are the main causes of mortality in patients undergoing hemodialysis. The presence of left ventricular hypertrophy (LVH), in turn, is an important independent factor in cardiovascular risk in patients with chronic kidney disease (CKD), including patients in hemodialysis [42, 26].

One of the factors contributing to improved survival of patients with preserved residual renal function, according to *Ma T.A. et al.* [26], there may be a positive effect of residual renal function, in particular residual diuresis, on left ventricular function in patients on hemodialysis. The presence of residual diuresis allows better control of the volume of blood circulation. According to the authors, left ventricular hypertrophy and systolic dysfunction in the group of patients with residual renal function were less severe than in the group without preserving residual renal function.

Thus, the concentration of total homocysteine and natriuretic peptide B in patients with residual renal function was reduced compared to patients with unsaved residual renal function and positively correlated with residual diuresis ($p < 0.0001$).

Together with other indices, in some literary sources as the predictor of mortality they also indicate phosphorus concentration in the blood serum. Wang M. et al. [45] they assume that the remainder function of kidneys influences the risk of mortality, connected with serum phosphorus and intact parathyroid hormone among the patients, who are found on hemodialysis.

A study conducted by the authors in the United States of America, with a sample of 35114 people, revealed that 8102 (23%) patients died during the first year of hemodialysis. As it became known, at higher serum phosphorus concentrations there was an increased risk of mortality, which, in turn, was expressed among patients with a higher residual clearance of renal urea ($P_{\text{interaction}} = 0.001$). Indicators of residual renal function were poorly connected with better survival in patients with elevated phosphorus levels. [45].

Some authors consider that the secretion of urine can serve as the simple indicator of the remainder function of kidneys in patients, who are found on hemodialysis. According to their data, the secretion of urine in the 1st year of hemodialysis, which testifies about the retention of the remainder function of kidneys, was independently connected with the lower mortality of all reasons on 35% (HR = 0,70; 95% CI (0,52-0,93); $p = 0,02$) and by tendency toward reduction in the mortality from the cardiovascular diseases (HR = 0,69; 95% CI (0,45-1,05); $r = 0,09$) [28].

A positive effect of urine volume even at very low concentrations was revealed in a single-center study conducted in the United States of America (USA). The authors suggest that urine output of more than 100 ml per day was associated with a 65% reduction in the risk of death over the next two years [34].

Evaluation of the effect of residual renal function with determination of urea clearance in studies conducted in the UK showed that in patients with urea clearance ≥ 1 ml / min after 6 months, mortality is 31% lower than in patients with urea clearance < 1 ml / min. [43].

As a result of a review of literary sources, we revealed that there are works whose purpose was to study the effect of dialysis frequency in relation to residual renal function on hemodialysis outcomes. It is estimated that the risk of mortality may increase or decrease the incidence of hemodialysis. Some studies have found that dialysis twice a week does not increase the risk of death compared with dialysis three times a week. In their opinion, a hemodialysis regimen twice a week is the best option in cases with preserved residual renal function [23].

Somewhat contradictory data obtained in its studies *Hwang H. S. et al.* [19]. Thus, the multidimensional model of the proportional risks of coke showed that in patients with the preserved remainder function of the kidneys, which transferred hemodialysis two times a week in comparison with the patients with the preserved remainder function of kidneys, who transferred hemodialysis three times a week, were the higher risk of the mortality (HR= 4,20; 95% CI (1,02–17,32), $r = 0,04$). The highest risk of mortality was

also observed in patients without residual renal function who underwent hemodialysis three times a week (HR = 5.04; 95% CI (1.39–18.33), $p = 0.014$). Further, the authors compared patients without retaining residual renal function who underwent hemodialysis three times (control group) per week with patients with preserved renal function who underwent dialysis twice a week. Patients of the second group, that is, with residual renal function and a hemodialysis regimen twice a week, had no less risk of mortality (HR = 0.83; 95% CI (0.34–2.01), $p = 0.68$). However, in patients with residual renal function who underwent hemodialysis twice a week, the volume of urine and Kt / V in the kidneys were greater than in patients with residual renal function who underwent hemodialysis three times a week. Based on the findings, the authors recommend that, when deciding on the frequency of hemodialysis, consider residual renal function.

Nevertheless, according to the results of other studies, hemodialysis twice a week had better preservation of residual renal function than three times a week [24, 47]. Thus, according to the authors, hemodialysis twice a week can provide a sufficient dose of dialysis, similar to dialysis three times a week, provided that the residual renal function is preserved.

It is believed that infrequent hemodialysis treatment can expose patients with chronic renal failure to several risk factors for cardiovascular diseases, including hypervolemia, hyperkalemia, and higher levels of calcium phosphate products [20, 33].

At the same time, residual renal function significantly contributes to reducing the risk of cardiovascular disease in patients on hemodialysis. [28, 31].

However, in many countries of the world, the dialysis frequency three times a week is considered the standard hemodialysis treatment regimen to achieve an adequate dialysis dose. According to the guidelines of the Kidney Disease Outcomes Initiative (KDOQI), hemodialysis treatment is recommended three times a week in patients without residual renal function. As for the issues of reducing the dialysis frequency, this is possible in cases with preserved residual renal function [19].

Conclusions and discussion

Thus, an analysis of literature on the study of factors affecting outcomes in patients with chronic renal failure undergoing hemodialysis showed that residual renal function is interrelated with better survival and a lower risk of mortality. In addition, urine volume, compared to other indicators of residual renal function, is the best predictor in determining outcomes in patients undergoing hemodialysis therapy.

Van Olden R.W. et al. [40] consider that urine volume per day is an effective indicator of assessing residual renal function. In their observations, the authors revealed a significant positive correlation between the glomerular filtration rate and the volume of urine collected per day.

There are other studies in which urine volume was used as the main indicator for determining the loss of residual renal function (urine output within 24 hours of less than 200 ml) [26, 36].

Also, as a result of a review of literary sources, we have revealed that there are other survival factors for patients on hemodialysis.

However, the opinions of researchers regarding the effect of the dose and frequency of dialysis on patient survival were controversial.

Unfortunately, in Russian-language databases, we have not found researches that study the factors of mortality or survival of patients with chronic renal failure undergoing hemodialysis. In our country, similar studies have not been conducted, in particular with the determination of residual renal function.

Since the assessment of residual renal function in patients with chronic renal failure undergoing hemodialysis is not an easy task, it is determined in less than 5% of patients. This, in turn, leads to an irrational approach to hemodialysis treatment and increased mortality [35]. In this regard, further research in this direction is necessary.

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