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REVIEW ARTICLE

Outcome of a Physical Rehabilitation Program on Functionality and Impact on Quality of Life in Postoperative Liver Transplant Patients: A Systematic Review

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ABSTRACT

Objectives: To conduct a systematic review of the literature on the outcomes of a physical rehabilitation program on functionality and identify possible impacts on quality of life in patients after liver transplantation. **Methods:** Controlled clinical trials and observational studies were selected from the PubMed, SciELO, and BIREME databases that fit the PICO (P – population; I – intervention; C – comparison; O – outcomes) question "what are the benefits of a physical rehabilitation program on functionality and quality of life outcomes in patients undergoing liver transplantation?" Studies written in English, Portuguese, and Spanish, published in the last 10 years were selected. After selection, the Physiotherapy Evidence Database (PEDro) scale was used to perform the methodological evaluation of the studies. **Results and Discussion:** A total of five interventionist articles were selected, most of which had good methodological quality. Only one study did not associate resistance training with aerobic exercises, but all had significant results regarding increased functional capacity and reduced perception of fatigue after liver transplantation. **Conclusion:** The studies indicated that the association of a resistance training program associated with aerobic training is beneficial in terms of muscle strength gain, exercise capacity, and perception of fatigue.

Descriptors: Liver Transplantation; Quality of Life; Functionality; Rehabilitation Program.

Desfecho de um Programa de Reabilitação Física sobre a Funcionalidade e Impacto na Qualidade de Vida em Pacientes no Pós-Operatório de Transplante Hepático: uma Revisão Sistemática

Objetivos: Realizar uma revisão sistemática da literatura acerca dos desfechos de um programa de reabilitação física sobre a funcionalidade e identificar possíveis impactos na qualidade de vida em pacientes no pós-transplante hepático (TxH). **Métodos:** Foram selecionados ensaios clínicos controlados e estudos observacionais das bases de dados PubMed, SciELO e BIREME que se encaixassem na estratégia PICO (P – *population*; I – *intervention*; C – *comparison*; O – *outcomes*) guiando a elaboração da pergunta norteadora: "quais os benefícios de um programa de reabilitação física sobre os desfechos de funcionalidade e qualidade de vida em pacientes submetidos ao transplante hepático?" Foram selecionados estudos escritos em inglês, português e espanhol, publicados nos últimos 10 anos. Após a seleção, a escala Physiotherapy Evidence Database (PEDro) foi utilizada para realizar a avaliação metodológica dos estudos. **Resultados e Discussão:** Foram selecionados cinco artigos intervencionistas, a maioria com boa qualidade metodológica. Apenas um estudo não associou o treino resistido a exercícios aeróbicos, porém todos tiveram resultados significativos quanto ao aumento da capacidade funcional e redução da percepção de fadiga no pós-TxH. **Conclusão:** Os estudos indicaram que a associação de um programa de treinamento resistido com treino aeróbico é benéfica quanto ao ganho de força muscular, capacidade de exercício e percepção de fadiga.

Descritores: Transplante Hepático; Qualidade de Vida; Funcionalidade; Programa de Reabilitação.

INTRODUCTION

The liver is an essential organ for vital homeostasis, acting in the degradation of toxic chemical residues, the excretion of bile, and the production of crucial proteins in coagulation factors. It is also the first storage site for nutrients from the intestine[1]. Consequently, it becomes susceptible to the deterioration of its functions, and an uninterrupted cycle of inflammation, degradation and regeneration of the hepatic parenchyma begins, giving rise to areas of fibrosis in the organ that, associated with cirrhosis, lead to chronic liver disease[2].

Liver transplantation (LTx) is the gold standard treatment for end-stage liver disease, revolutionizing the treatment of these diseases. However, it is essential to highlight that the process of performing an organ transplant responds to a set of critical factors, considering the increasing number of patients requiring this therapy compared to the number of organs available for donation[2]. In Brazil, the transplant process, financed and provided entirely by the Unified Health System (Sistema Único de Saúde-SUS) and internationally recognized, offers comprehensive and free pre- and post-transplant assistance to the patient[3,4].

As a significant surgical procedure, LTx requires multiple care measures in the immediate postoperative period, as compromises to the hemodynamic and respiratory systems are frequent[5]. Such situations also occur in other abdominal surgeries; however, the literature describes little regarding postoperative functionality impairments. Lifestyle habits such as alcoholism and smoking impact postoperative recovery, as do pre-existing comorbidities, patient age and surgical time, which can prolong hospitalization time and result in limited functional capacity[6].

Due to disease progression during pre-transplantation, patients tend to develop fatigue and frailty criteria due to low activity levels and low physical fitness, leading to sarcopenia[7]. Sarcopenia is established when there is a reduction in muscle mass measurement, just as frailty is characterized by impairment of muscle function, assessed using functionality scales. Both are markers for adverse outcomes in cirrhotic patients[8].

Physical rehabilitation programs have been applied to post-organ transplant patients to positively impact various outcomes, such as length of hospital stay and morbidity and mortality[9,10]. However, clinical practice needs more consensus regarding specific protocols for liver transplant patients and their possible benefits. Therefore, the objective of this study was to conduct a systematic review of the literature, evaluate the outcomes of a physical rehabilitation program on functionality and identify possible impacts on the quality of life in this patient profile.

METHODS

The present is a systematic literature review in which a specific flowchart was followed to organize and detail the search process in databases, with their respective quantities, evaluation and selection for the review, providing greater integrity to the data reported.

The PICO strategy (P – population; I – intervention; C – comparison; O – outcomes) guided the elaboration of the guiding question: "What are the benefits of a physical rehabilitation program on the outcome of functionality and quality of life in patients undergoing liver transplantation?".

Search strategiesa

A researcher conducted a data search in the PubMed/Medical Literature Analysis and Retrieval System Online (MEDLINE), BIREME and SciELO databases from May to August 2023. The search included English, Portuguese, and Spanish studies published in the last ten years.

Three search flows were used to perform the search in Descritores em Ciências da Saúde (DECS), in English and Portuguese, in a combined form:

Flow 1: We used the descriptors "Qualidade de vida", "Reabilitação", "Funcionalidade", "Transplante hepático" and "Adulto", associatedly, using boolean operators AND, OR e NOT.

Flow 2: "Funcionalidade", "Programa de reabilitação", "Transplante hepático", and "Adulto" were used associated with the Boolean operators OR and AND, followed by NOT and "Pediatria".

Flow 3: Were used "Qualidade de vida", "Programa de reabilitação", "Transplante hepático" and "Doadores" associated by Boolean operators OR, AND and NOT.

Eligibility criteria and selection of articless

Controlled clinical trials and observational studies were selected. The PICO strategy was applied to select the articles: adult patients undergoing LTx performed on living or deceased donors (population), physical rehabilitation program (intervention), other treatments or no intervention (comparison), improving functionality and quality of life (outcomes).

Articles published in English, Portuguese and Spanish, with full texts and available electronically, were eligible for inclusion. However, all review studies, those that did not present a full online abstract for analysis, and those conducted with children and adolescents were excluded.

The researcher read the titles of the articles initially identified, followed by the abstracts and full texts, applying the inclusion criteria to select those that comprised the sample.

Data extraction and analysis

The data were organized in Table 1 according to the PICO strategy. Authorship, year of publication, type of study, data on the population studied, proposed intervention and, finally, the primary outcomes found in the articles were extracted.

Table 1. General information extracted from the studies selected to compose the review.

Author	Study type	Population (P)	Intervention (I)	Comparison (C)	Outcomes (O)
Ergene et al.[11]	RCCT	30 LTx recipients (10 F and 20 M), age 51.5 ± 15.4, from the immediate postoperative period with hemodynamic stability and spontaneous breathing.	Training group (TG): standard physiotherapy associated with resistance training, lasting 20 minutes, twice a day, five days a week, in the initial two weeks, during the hospitalization period, and six weeks with unsupervised home training, for eight weeks.	CG: preoperative education, standard postoperative physiotherapy with early mobilization, assisted active exercises, and breathing exercises.	The program had good adherence (96.8% attendance). On the second postoperative day, the TG walked in the hallway, increasing the distance covered in the 6-minute walk test but without significant differences between the groups.
Totti et al.[12]	NRCCT	29 LTx recipients (6 F and 23 M), age 52 ± 8 years, transplanted more than six months ago.	Group A: aerobic and strength training lasting 1 hour, three times/week, for 12 months, in a specialized center supervised by exercise specialists.	Group B: general recommendations for home exercises without specific supervision.	Training that combines aerobic and strength exercises can be a tool for gaining strength, controlling glucose metabolism and improving quality of life in patients undergoing LTx.
Maffei et al.[13]	NRCCT	40 LTx recipients (9 F and 31 M), age 52 ± 9 years, from the immediate postoperative period.	Experimental group (EG): conventional physiotherapy associated with a training program ranging from assisted resistance and aerobic training (depending on the post-LTx phase, twice a day, five days/week, during the hospitalization period).	CG: care initiated after medical prescription, depending on the patient's progress, once a day, lasting 10 to 15 minutes.	EG participants sat at the bedside earlier and more often than CG. The early rehabilitation program was tolerable and effective in the ICU setting.
Moya-Nájera et al.[14]	RCCT	54 LTx recipients (5 F and 49 M), age 55.3 ± 9.2 years, transplanted six months ago.	Intervention group (IG): combined resistance and aerobic exercise training, lasting 75 minutes, twice a week, for 24 weeks, carried out in the hospital, under the supervision of specialists.	CG: recommendations and guidelines for usual care, with light physical activity, without specifying duration, heart rate or intensity of exercise.	The IG evolved with a significant improvement in global strength compared to the CG and substantial improvements in quality of life and functional status.
Van Den Berg-Emons et al.[15]	OS	18 LTx recipients (8 F and 10 M), age 51 ± 9.9, transplanted more than one year ago and who met fatigue criteria.	Aerobic and strength training, lasting 1 hour, twice a week, for 12 months, with specialist supervision.	Paired before treatment. There was no CG.	Participants completed the training program with significantly improved fatigue and knee flexor muscle strength.

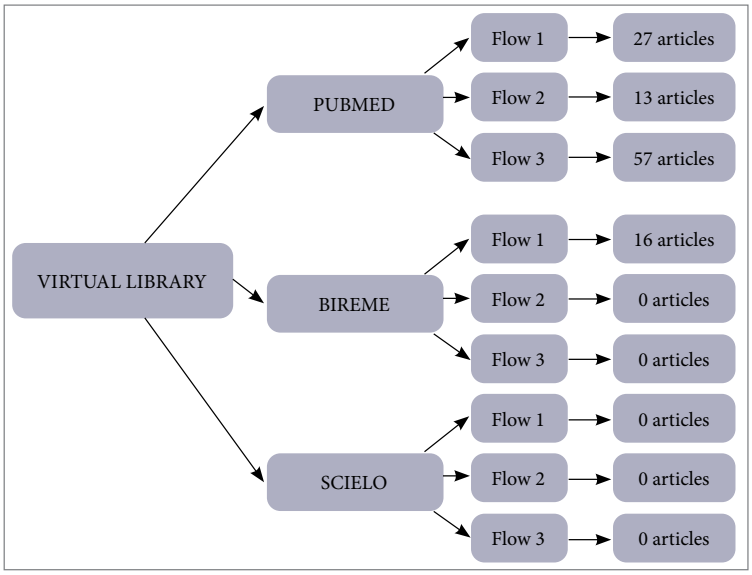
Source: Elaborated by the authors. NRCCT = non-randomized controlled clinical trial; RCCT = randomized controlled clinical trial; OS = observational study; M = male; F = female; LTx= liver transplant.

Analysis of methodological quality

The methodological quality of the included articles was assessed according to the Physiotherapy Evidence Database (PEDro) scale, which aims to classify clinical trials that evaluate physiotherapists' clinical practice interventions. This scale consists of 11 criteria, each receiving a score in the study, except for criterion 1, which is not scored. Thus, the minimum score is 0, while the maximum is ten points[16]. For randomized controlled trials with complex interventions, such as an exercise protocol, a score of 8/10 is considered excellent[17]. One evaluator conducted the evaluation, and a second evaluator was consulted in case of doubt.

RESULTS

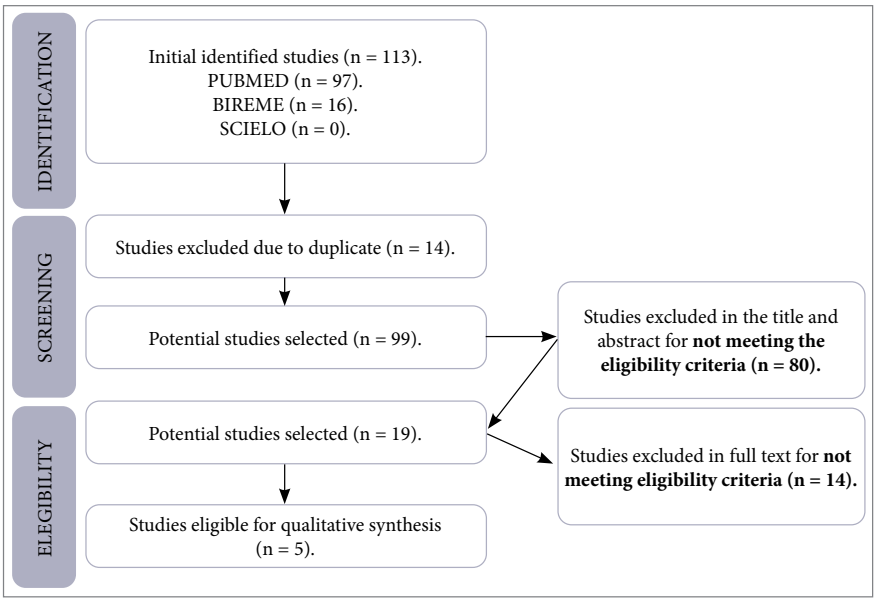
As described in Fig. 1, 113 eligible articles were initially selected for evaluation using the three flows as search strategies.



Source: Elaborated by the authors.

Figure 1. Quantities selected in each database.

Of the three databases selected for searches, PubMed yielded the most results. Twenty-seven articles were selected using flow 1, 13 articles using flow 2, and 57 articles using flow 3. The BIREME database yielded 16 articles selected only by flow 1. No articles became eligible in searches from flows 2 and 3. Finally, the SciELO database yielded no articles eligible for evaluation in any of the three flows. A flowchart was constructed that stratifies and quantifies the articles for final selection (Fig. 2).



Source: Elaborated by the authors

Figure 2. Article selection flowchart

The initial selection was made by reading the titles, resulting in 113 selected articles. Of these, 14 studies were excluded due to duplicates. After reading the titles and abstracts, 80 articles were excluded because they needed to meet the eligibility criteria. Finally, after thoroughly reading the complete text, five articles were selected to compose the final sample, as shown in Table 1.

Data were collected from 171 participants distributed among the five studies. Males accounted for the majority of the sample, with 133 participants. All five studies used resistance training in their protocols, but only three associated it with aerobic exercise. The training frequency varied from two to five times weekly, lasting 20 to 75 minutes per session. Finally, the period in which interventions through rehabilitation protocols were performed varied from the first postoperative day to the follow-up period of 18 months after LTx.

Table 2 shows the methodological quality scores of the selected studies. Only the most recent study scored excellent methodological quality. Three other studies scored good quality, and only one scored low methodological quality.

Table 2. Analysis of the methodological quality of studies using the PEDro scale.

PEDRo Scale Items	Ergene et al.[11]	Totti et al.[12]	Maffei et al.[13]	Moya-Nájera et al.[14]	Van Den Berg-Emons et al.[15]
1. Have eligibility criteria been specified?*	Yes	Yes	Yes	Yes	Yes
2. Were the subjects randomly assigned to groups (in a crossover study, subjects were randomly assigned to groups according to the treatment they received)?	Yes (1)	No (0)	No (0)	No (0)	No (0)
3. Was the allocation of subjects secret?	Yes (1)	No (0)	No (0)	No (0)	No (0)
4. Were the groups initially similar concerning the most important prognostic indicators?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)
5. Were all subjects blinded to the study?	Yes (1)	No (0)	No (0)	No (0)	No (0)
6. Were all therapists who administered the therapy blinded?	Yes (1)	No (0)	No (0)	No (0)	No (0)
7. Did all assessors who measured at least one key outcome do so blindly?	No (0)	No (0)	No (0)	No (0)	No (0)
8. Were measurements of at least one key outcome obtained in more than 85% of the subjects initially assigned to the groups?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
9. Did all subjects from whom outcome measurements were presented receive the treatment or control condition as allocated, or, where this was not the case, were data analyzed for at least one of the key outcomes on an "intention to treat" basis?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
10. Were the results of intergroup statistical comparisons described for at least one key outcome?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
11. Does the study present precision and variability measures for at least one key outcome?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
Total score	**9/10**	**5/10**	**5/10**	**5/10**	**4/10**

Source: Elaborated by the authors. *Item does not count towards the final score.

All studies increased the strength of the main muscle groups and aerobic capacity, even those that did not associate with aerobic training. Only one study did not evaluate factors such as perception of fatigue and perception of health, but the others showed improvements at the end of the training program. Two studies resulted in improved quality of life of liver recipients.

DISCUSSION

There are many expectations about what life will be like after LTx, but the literature is still scarce regarding criteria for quality of life and functionality in post-transplant life. This study sought to summarize the possible benefits of a physical rehabilitation program to functionality in post-liver transplant patients. All selected studies used resistance training in their protocols, but three associated aerobic exercises with the protocol.

Based on this assumption, Maffei et al.[13] randomized their participants into two groups to validate the feasibility and tolerance of an intensive rehabilitation protocol initiated during the postoperative period in the intensive care unit (ICU) of liver transplant recipients. For the experimental group (EG), a care protocol associated with conventional physiotherapy care was implemented. In contrast, the control group (CG) received only conventional physiotherapy, following the medical prescription, with 10 to 15-minute

sessions once a day. The EG protocol was divided into three phases, starting with passive mobilizations while the patient was still sedated and on mechanical ventilation.

As findings, the EG adopted the "sitting at the bedside" posture earlier and more often than the CG (EG: 106 times and CG 27 times; 2.61 ± 8 vs. 9.7 ± 13 days; p = 0.48, respectively), perhaps because they started intense mobilizations early. There was a tendency for a shorter ICU stay in the EG but without significance13. Also using early mobilization, a Chinese study evaluated the effects of early mobilization after kidney transplantation. Despite being in a different audience than that assessed in this review, the EG resulted in drain removal earlier than the CG, and ambulation also occurred earlier than in the CG[18]. Em ambos os estudos, observou-se redução do tempo de internação hospitalar no GE.

Although it is not related to the length of the patient's stay in the ICU, early mobilization is recommended by the Brazilian guidelines for early mobilization as the primary goal for the multidisciplinary team, with the main objective of achieving the best functional stage at the time of discharge from the ICU[19]. Functional assessment is vital at the time of discharge from the ICU when we understand that liver patients present several physical symptoms before LTx, such as muscle weakness and fatigue, directly affecting functional status after transplantation.

In a pioneering move, Van Den Berg-Emons et al.[15] initiated a study of post-LTx functionality. This study brought together 18 post-transplant and fatigued participants for a 12-week follow-up whose training consisted of an interval circuit of aerobic training and resistance exercises. The authors used three scales to measure the progression of fatigue and its temporality, namely: the Fatigue Severity Scale (FSS), which assesses the impact of fatigue on daily functioning; the Horizontal Visual Analog Scale (VAS), which analyzes fatigue in general over the last month; and the Checklist Individual Strength (CIS-Fatigue), which assesses feelings of fatigue experienced in daily life in the previous two weeks.

The participants were reassessed after 12 weeks, and a significant improvement in the fatigue perception score on the three scales was evident. In addition, the age of the individuals with severe fatigue was much lower after the program (22-53% lower). The study also resulted in significant strength gains in the knee flexor muscles and improved aerobic capacity. Overall, the study significantly reduced fatigue and increased functional capacity at the end of the program[15].

Ergene et al.[11] randomized 30 patients equally into two groups; both received standard physical therapy, but only the intervention group combined the treatment with a resistance training protocol for the main muscle groups. Monitoring was supervised during two weeks of hospitalization and continued remotely via telephone calls after hospital discharge. The evaluation was carried out in detail by dynamometry and manovacuometry, collecting data on peripheral and respiratory muscle weakness. Functional tests were also used, such as the 6-minute walk and the 30-second sit-to-stand test associated with the CIS-Fatigue. After four weeks of training, the participants in the EG already demonstrated improvement in muscle strength, mainly in the deltoid group and in the general perception of fatigue. At the end of 8 weeks of the protocol, the EG showed significant improvement in generalized muscle strength, including the respiratory muscles. Although aerobic training was not part of this protocol, there was a prevalence of the beginning of walking in the hallway on the 2nd postoperative day in both groups; however, 86.7% of the training group showed an increase in the distance covered in the 4th week, compared to the initial evaluation[11]. This finding indicates that gaining muscle strength improves functional capacity and exercise perception.

Interestingly, much of the program was conducted with continued training at home and without direct supervision. Still, even so, it resulted in significant functional improvement. Thus, it is assumed that it is possible to create and continue rehabilitation at home without direct supervision when patients take ownership of their recovery process and are well-trained.

However, whether the results would have been even better or earlier if the training program had been fully supervised is still being determined. Totti et al.[12] used this prerogative to evaluate the difference between home training (C G) and supervised training (E G). Similarly, Moya-Nájera et al.[14] previously performed a resistance and aerobic interval exercise protocol in liver recipients. Both used incremental testing to assess aerobic capacity, as well as the Short Form Health Survey Questionnaire (SF-36) to assess self-reported health status, assessing aspects of physical functioning, role limitations due to physical health, pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health.

Both studies resulted in improvements in muscle strength and perception of fatigue. Still, Totti et al.[12] (2019) brought an exciting improvement in metabolism and glycemic control in the EG compared to the CG. This result is noteworthy since metabolic disorders such as hypertension and diabetes are associated with mortality in the first years after LTx[20].

According to scientific literature, factors such as functionality and quality of life in patients who underwent LTx are closely related to the living conditions and the degree of impairment achieved while they were waiting for the transplant. An American study reports that the main limiting factor for exercise perceived by 70% of its listed patients was physical fatigue, followed by ascites and medications used in treatment. There is no quick and easy solution to the issue of fatigue, but practicing physical activity and participating in structured training can positively impact its perception, with improved muscle performance and participation in activities of daily living[21].

The limitations of this study include the exact timing of when the protocol began among the selected authors, which leaves a considerable margin for defining the ideal time to start training. Another area for improvement is that the samples were mainly composed of men, making it impossible to standardize the data. A more robust study with a more balanced sample is necessary. Finally, psychosocial and emotional factors and their impacts on physical capacity were not evaluated.

CONCLUSION

Based on the discussion, a resistance training program brings satisfactory results regarding strength gain and overall functional capacity. When aerobic training was combined with resistance training, it resulted in an improvement in the perception of fatigue and a reduction in the prevalence of severe fatigue after the protocol. However, more robust studies with greater methodological rigor are still needed to support these findings.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Conception and design: Falcão TN, Farias VX; **Methodology:** Falcão TN, Farias VX; **Investigation:** Falcão TN, Farias VX; **Data curation:** Falcão TN, Farias VX; **Supervision:** Cardoso MES, Vasconcelos RS, Farias VX; **Article writing:** Falcão TN, Farias VX; **Critical revision:** Cardoso MES, Vasconcelos RS, Farias VX; **Final approval:** Falcão TN, Cardoso MES, Vasconcelos RS, Farias VX.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable.

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