



UNIVERSIDADE DE
COIMBRA

FACULDADE
DE
MEDICINA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

MARIA JOÃO DE CASTRO QUINTELA MADEIRA CARDOSO

***Is Cholecystectomy really Harmful? - a Long-Term Quality
of Life Study in Living Donor Liver Transplantation***

ARTIGO CIENTÍFICO

ÁREA CIENTÍFICA DE CIRURGIA

Trabalho realizado sob a orientação de:
PROFESSOR DOUTOR HENRIQUE ALEXANDRINO
DR. PEDRO OLIVEIRA

SETEMBRO 2019

**Is Cholecystectomy really Harmful? – a Long-Term Quality of Life Study in
Living Donor Liver Transplantation**

Maria João de Castro Quintela Madeira Cardoso¹

Henrique Alexandrino^{1,2,4}

Pedro Oliveira^{1,3}

¹: Faculdade de Medicina - Universidade de Coimbra

²: Serviço de Cirurgia Geral – Centro Hospitalar e Universitário de Coimbra

³: Unidade de Transplantação Hepática Pediátrica e de Adultos – Centro Hospitalar e
Universitário de Coimbra

⁴: *Institute for Clinical and Biomedical Research* – Universidade de Coimbra

E-mail – mariajoao.madeiracardoso@gmail.com

Coimbra, Setembro de 2019

Table of Contents

NOTA PRÉVIA	5
AGRADECIMENTOS	8
LIST OF ABBREVIATIONS	8
ABSTRACT	14
RESUMO.....	15
INTRODUCTION.....	17
MATERIALS AND METHODS	19
RESULTS.....	26
GLOBAL QUALITY OF LIFE (SF-36).....	26
GASTROINTESTINAL QUALITY OF LIFE (GIQLI).....	30
ABDOMINAL WALL-RELATED QUALITY OF LIFE (EURAHS) AND PHYSICAL ACTIVITY LEVEL (IPAQ)	32
DISCUSSION	34
CONCLUSION.....	38
REFERENCES.....	39
OUTROS TRABALHOS / APRESENTAÇÕES	42

Nota Prévia

A presente Tese é muito mais do que o resultado de uma extensa pesquisa bibliográfica ou de um conjunto de resultados interpretados de forma rigorosa e científica; é também o reflexo de dois anos de trabalho, aprendizagem e crescimento.

Quando me desafiaram a estudar o Dador Vivo de Fígado nada sabia sobre o tema. Recordo-me de partilhar com o meu Orientador que precisava de fazer uma pesquisa antes de poder aceitar o desafio, uma vez que sempre quis fazer a minha primeira Tese sobre algo com que me identificasse e que tivesse um significado para mim. Li vários artigos sobre morbi-mortalidade e qualidade de vida dos Dadores Vivos, todos eles cientificamente rigorosos e metódicos, mas, apesar de já o esperar, nenhum respondeu à minha maior questão: mas afinal quem são estas pessoas que doam parte do seu fígado aos seus filhos, sobrinhos e outros? Talvez tenha sido esta a principal razão para me ter debruçado sobre este tema.

Apesar de ter percorrido um longo caminho até encontrar todas as ferramentas que fazem parte dos métodos desta Tese, considero que o verdadeiro ponto de partida para este trabalho ocorreu no dia em que contactei pela primeira vez com um Dador. Recordo-me como se fosse hoje, estávamos só os dois e eu procurava, a todo o custo, seguir os questionários e não dispersar. Havia perguntas nos questionários que me deixavam apreensiva e receosa como “O recetor está vivo? De boa saúde?” ou então, e esta assustava-me particularmente, “Se pudesse voltar atrás, doaria novamente?”. É fácil saber o que dizer quando as respostas são positivas, mas... e se não forem? Enquanto aluna, a minha experiência em comunicação com doentes está ainda a iniciar-se e, apesar de nas primeiras entrevistas ter recebido respostas com as quais me sentia confortável, sabia que mais tarde ou mais cedo iria ter que lidar com o outro lado do Dador Vivo.

Todos os Dadores me tocaram, mas houve dois que me marcaram particularmente. Vou chamar-lhes João e Miguel.

O João é um jovem pouco mais velho que eu, tem uma menina a quem doou, sem pensar duas vezes, parte do seu fígado. Recordo-me de me ter falado do quão difícil foi voltar à vida ativa depois da cirurgia, não por questões de saúde, mas sim pela falta de capacidade dos outros para compreenderem que tinha sido submetido a uma intervenção cirúrgica major da qual não precisava. Dizia-me que se sentia sem apoios

externos e que a situação no trabalho estava cada vez mais complicada, estava preocupado. Já sabia que a resposta à primeira pergunta acima mencionada seria positiva e tinha a certeza que o João voltaria a doar sem qualquer dúvida. O que não estava à espera era que quando o questionasse sobre a incisão abdominal e o seu resultado estético, olhasse para mim perplexo com a pergunta, como quem não compreende como é que alguém se pode importar com a questão estética, e me respondesse que a enorme incisão no seu abdómen tinha muito significado para ele, vendo-a como uma tatuagem que partilha com a filha e que os unirá para sempre, dada a semelhança entre as cicatrizes dos dois. Achei isto lindíssimo.

O Miguel é um jovem muito ativo, tem um filho e doou parte do seu fígado à sua sobrinha. Quando o vi pela primeira vez, passavam seis meses desde a cirurgia, queixava-se que ainda não tinha conseguido voltar à sua vida em pleno, não conseguia fazer o desporto que estava habituado, não conseguia brincar com o seu filho por causa dos esforços físicos, mas parecia encarar tudo de forma positiva. Novamente, respondeu-me aquilo que eu mais desejava ouvir: que a bebé estava viva e de boa saúde e que doaria novamente. Passados dois meses, soube que a bebé havia falecido. O Miguel veio novamente à consulta do meu Orientador e tive a oportunidade de falar com ele um bocadinho. Não tive coragem de lhe fazer a primeira pergunta, já sabia que a resposta seria “não”. No entanto, deixei o nervosismo e o receio de lado, e senti-me à vontade para o questionar: “Miguel, e agora, doaria novamente?”. Ele ficou parado a olhar para mim como se não percebesse a minha dúvida e respondeu-me: “Claro, apesar de a menina ter falecido, tenho a certeza que se fez tudo o que estava ao nosso alcance e, além disso, pude dar aos pais mais um tempinho feliz com ela”. Depois deste dia fiz questão de me manter a par do estado físico e psicológico do Miguel, sei que vai tendo altos e baixos, tem tido dificuldade em lidar com o triste desfecho, mas acaba sempre por me dizer que valeu a pena.

Ao longo dos últimos meses fui-me apercebendo que os Dadores são pessoas especiais, olham para o que os rodeia de forma diferente, valorizam cada pequena coisa da vida e, acima de tudo, são um exemplo de altruísmo e coragem. Um dia o meu Orientador disse-me que, enquanto cirurgiões, temos um poder terrível por, com um bisturi, podermos agredir outro ser humano, com o seu consentimento, na esperança de lhe trazer benefício. Os Dadores são submetidos a uma intervenção cirúrgica major da qual não beneficiam diretamente. Daí que devamos ter presente, mais do que nunca, o princípio da medicina *Primum non nocere* e que estudar o verdadeiro impacto desta cirurgia seja tão importante, quer para garantir a sua segurança, quer para lhes poder

responder com maior certeza a algumas questões que possam ter antes de aceitar este desafio.

Tenho vindo a refletir e, não será, na verdade, o Transplante Hepático de Dador Vivo o maior benefício das suas vidas? Penso que sim. Os Dadores tem algo que os distingue das outras pessoas, todos eles passaram por altos e baixos, muitos viram o desfecho sorrir-lhes, outros tiveram que encarar a perda e, por vezes, a sensação de ter sido em vão, mas acredito que são essas mesmas características que os tornam únicos que os fazem ultrapassar as adversidades e, no fim de tudo, afirmarem que doariam de novo e encontrarem finalmente a paz.

Este trabalho, como disse acima, significa muito mais que um estudo de qualidade de vida gastrointestinal. Além de ter contribuído em muito para a minha formação científica, mudou-me, quer enquanto futura médica, quer enquanto pessoa. Com esta Tese apercebi-me da fragilidade do ser humano e de como é grande a nossa responsabilidade enquanto médicos. Foi difícil, semana a semana, manter a postura rigorosa de cientista e não permitir que as emoções entrassem em campo para que o trabalho fosse realizado com máxima clareza de raciocínio e da forma objetiva que esta Tese exigia. No entanto, nunca deixei de pensar nos Dadores e em tudo o que me ensinaram, deixei sim que essas emoções fortes fossem o motor para a minha motivação, dedicação e empenho na realização deste trabalho, sobretudo porque os Dadores assim o merecem.

O caminho percorrido até aqui não podia ter sido mais gratificante, sinto que não só me marcou a mim, como aos que caminharam lado a lado comigo, trilhando sempre aquele que acredito ser o caminho justo e correto.

E assim termino, concluindo que esta é a Tese que eu quis escrever e com a qual me identifico.

Os Dadores são, de facto, seres humanos especiais.

Agradecimentos

Apesar de muitos terem contribuído significativamente para a realização da presente Tese de Mestrado, prestando o seu mais sincero apoio, infelizmente, não posso enumerar todos. Assim, aqui deixo o meu tributo àqueles cujo papel foi determinante e sem os quais nunca teria sido possível ultrapassar todas as etapas que culminaram neste trabalho.

Em primeiro lugar, gostaria de expressar a minha profunda gratidão ao Professor Doutor Henrique Alexandrino, ilustre Professor Auxiliar da Faculdade de Medicina da Universidade de Coimbra, exímio Cirurgião, meu Orientador Científico e Mestre e, depois de dois anos de trabalho em conjunto, Amigo. Não posso deixar de referir a minha enorme admiração pela sua capacidade de trabalho, rigor científico e profissional, dedicação aos Doentes, ao Hospital e à Universidade, bem como pela sua busca incessante e contagiante pelo conhecimento. Recordo a forma desafiante como, em 2017, me lançou o convite para me debruçar sobre o tema desta Tese. No início, tive algum receio de não conseguir corresponder às expectativas, mas rapidamente me fez deixar a insegurança de lado, quer pela motivação, quer pela constante partilha da sua entrega e entusiasmo pela investigação e pela fascinante área da Cirurgia Hepatobiliar. Tive a sorte e a oportunidade de privar com o Professor Doutor Henrique Alexandrino na sua consulta, de onde pude extrair as maiores competências que levo do meu percurso académico, quer enquanto clínico, ensinando-me e ajudando-me a desenvolver algoritmos de raciocínio e de diagnóstico, quer enquanto ser humano, pelos valores que defende e pela forma serena e honesta com que nunca baixa os braços em busca do caminho justo e correto. Como em tudo, existem lacunas no ensino médico; no entanto, fico descansada por saber que procura a mudança necessária, contribuindo para a aquisição de competências clínicas e não clínicas dos alunos, culminando na formação de médicos mais capazes. Assim, não posso deixar de expressar a minha sincera gratidão por todas as oportunidades e projetos, pela motivação e disponibilidade, pela forma como me guiou neste caminho, por todas as idas ao bloco e ao Serviço de Urgência, pelas consultas, pelas críticas pertinentes e construtivas e, sobretudo, por acreditar em mim, pelas palavras certas nos momentos determinantes e por me ensinar muito mais que Medicina e Cirurgia. Que este seja o primeiro de muitos outros trabalhos e que continuem a surgir perguntas às quais queremos responder. O Professor Henrique Alexandrino constitui e constituirá sempre um Exemplo para mim e seria para mim uma enorme honra, um dia mais tarde, poder pertencer à sua equipa.

Em segundo lugar, não posso deixar de agradecer ao meu Coorientador, Dr Pedro Oliveira, Assistente Convidado da Faculdade de Medicina da Universidade de Coimbra e Cirurgião da Unidade de Transplantação Hepática Pediátrica e de Adultos dos Hospitais da Universidade de Coimbra pelo voto de confiança em mim depositado desde o início e ainda, em particular, pelo sólido contributo para os métodos desta Tese, que muito enriqueceram este estudo.

Gostaria igualmente de destacar a figura do Dr. Emanuel Furtado, Coordenador da Unidade de Transplantação Hepática Pediátrica e de Adultos dos Hospitais da Universidade de Coimbra. Não posso deixar de expressar o meu agradecimento por ter permitido a realização deste estudo e pelas críticas construtivas, cujo contributo para a discussão e enriquecimento da presente Tese foram fundamentais. Gostaria ainda de afirmar a minha enorme admiração pelo trabalho que desenvolve, diariamente, na Transplantação Hepática e cuja marca é notável em todos os doentes com quem tive a oportunidade de contactar.

Reconheço também o Dr. Hélder Carvalho, Diretor do Serviço de Cirurgia dos Hospitais da Universidade de Coimbra pela forma como coordena este Serviço, preservando-o como Centro de Referência que é. Gostaria de lhe agradecer por ter autorizado este estudo, permitindo o levantamento dos processos clínicos no que à população de Doentes de controlo concerne.

Destaco igualmente a figura do Professor Doutor Guilherme Tralhão, Professor Catedrático da Faculdade de Medicina da Universidade de Coimbra e Coordenador da Unidade de Cirurgia Hepato-bilio-pancreática dos Hospitais da Universidade de Coimbra. Indiscutivelmente um exemplo como clínico, investigador e docente, dotado de uma notável capacidade de trabalho, rigor e vocação para o ensino.

Não consigo imaginar o início deste trabalho sem o impulso da Dra. Ana Oliveira, Assistente Convidada da Faculdade de Medicina da Universidade de Coimbra, Cirurgiã da Unidade Colo-Rectal dos Hospitais da Universidade de Coimbra e, acima de tudo, a minha Professora de Propedêutica Cirúrgica e Amiga. A Dra. Ana Oliveira constitui um exemplo enquanto Médica Cirurgiã, quer clinicamente, quer ao nível da relação médico-doente. Nunca me esquecerei de como, no terceiro ano, me inspirou e me fez apaixonar pela cirurgia. Todo o meu gosto e interesse por esta área se deve à forma entusiasmante como me transmitiu os conhecimentos clínicos e à sua dedicação em cada aula, com cada doente, para com cada aluno. Gostaria ainda de lhe agradecer por todas as horas

de consulta, urgência, bloco e enfermagem que tive a oportunidade que partilhasse comigo. E ainda pela disponibilidade e prontidão com que aceitou, por dois anos consecutivos, orientar-me nos Estágios de Verão, recebendo-me e integrando-me na sua equipa da melhor forma possível. Para mim, a presente Tese não faria sentido sem a presença e contributo da Dra. Ana Oliveira. Aqui lhe presto toda a minha gratidão pela disponibilidade, pela confiança, pela atenção e pelos conselhos sábios e amigos que me deu, não apenas ao longo do desenvolvimento desta Tese, mas também ao longo de todo o meu percurso académico. Espero, um dia, poder vir a ter a oportunidade de trabalhar com a Dra. Ana Oliveira. É e será sempre, para mim, o principal motivo de me ter apaixonado pela Cirurgia.

Como não poderia deixar de ser, fica aqui uma palavra muito especial a todos os Colaboradores e Cirurgiões do Serviço de Cirurgia do Centro Hospitalar e Universitário de Coimbra, em particular, ao Dr. Marco Seródio, ao Dr. Luís Ferreira, ao Dr. Ricardo Martins, ao Dr. Miguel Fernandes, à Dra. Eva Santos e à Dra. Maria João Koch. E expressar-lhes a minha sincera gratidão pela forma incrível e disponível com que sempre me receberam no Serviço e me integraram nas suas atividades. São, sem dúvida, Médicos como estes que me fazem, dia após dia, urgência após urgência, ter a certeza de que a Cirurgia, apesar de difícil, é o caminho que quero seguir, sem nunca desistir ou baixar os braços.

De igual forma, expresso aqui o meu tributo a todos os Colaboradores da Unidade de Transplantação Hepática dos Hospitais da Universidade de Coimbra, em particular ao Dr. Carlos Bento, à Professora Doutora Francelina Lopes, à Dra. Sandra Pereira e à Dra. Susana Nobre pela amável forma com que sempre me receberam e pela análise crítica e pertinente ao longo deste percurso. Não posso deixar de expressar a minha admiração pela atividade clínica que diariamente desenvolvem com os doentes pediátricos e seus pais.

Não posso deixar de mencionar o nome da Dr. Vera Vieira, Cirurgiã do Hospital da Figueira da Foz, por ter sido a primeira pessoa a dedicar-se ao estudo do Dador Vivo de Fígado e por ter permitido a continuação do seu trabalho, resultando na presente Tese.

Destaco ainda a pessoa da Professora Doutora Bárbara Oliveiros, Professora de Bioestatística da Faculdade de Medicina da Universidade de Coimbra, cujo apoio e disponibilidade foram notáveis ao longo desta Tese.

Gostaria ainda de referir a pessoa do Dr. Fernando Manata, Cirurgião Geral do Serviço de Cirurgia do Centro Hospitalar e Universitário de Coimbra, cujo contributo para o meu conhecimento cirúrgico foi inegável no meu quarto ano. Apesar de não ter tido um papel diretamente relacionado com esta Tese, não posso deixar de lhe agradecer pelo apoio constante e, acima de tudo, por acreditar em mim e me estimular a ser cada vez melhor, desafiando as minhas capacidades e ajudando-me a nunca desistir. Obrigada por me incentivar tanto a trilhar um caminho na Cirurgia e por me fazer sentir recebida de braços abertos se, um dia, o meu percurso passar pelos Hospitais da Universidade de Coimbra.

À minha Família, em particular à minha Mãe, pelo amor, apoio incondicional em todas as horas e incentivo em todos os momentos da minha vida. Reconheço-lhe não só uma capacidade de trabalho inigualável, mas também a força ímpar com que luta contra as adversidades, sem nunca baixar os braços e que me contagia e me impele a nunca desistir. Ao meu Pai, maior defensor dos Direitos Humanos e cuja doença foi a grande responsável pela minha vocação enquanto Médica. E que, apesar de não poder estar presente em vida comigo, está e estará sempre no meu coração. Aos meus Avós, em particular ao meu Avô, o meu primeiro doente. E ao Rui, por estar sempre lá.

Aos meus Amigos que estão comigo nos bons e nos maus momentos, e que encontram constantemente forma de me presentear com um enorme apoio e carinho. Obrigada às minhas meninas, Joana, Martina, Sofia e Manuela, e ainda ao André e ao Francisco. Ao Gonçalo, por todo o apoio, encorajamento, sinceridade e carinho. O caminho percorrido até aqui não seria o mesmo sem a presença de todos.

Aos Secretários da Unidade de Transplantação Hepática Pediátrica e de Adultos do Centro Hospitalar e Universitário de Coimbra, Sr. Carlos e, em particular, à D. Manuela Pacheco, cujo papel foi fundamental no desenrolar deste trabalho. Sem a sua força, dedicação e disponibilidade, nunca teria conseguido contactar com todos os Dadores. Não posso deixar de destacar a forma profissional, rigorosa e amável com que, todos os dias, faz o seu trabalho. A D. Manuela é, sem dúvida, alguém com uma notável capacidade de chegar ao outro, ouvi-lo e presenteá-lo com uma palavra amiga.

Porque para último fica o mais importante, expresso o meu profundo e sincero reconhecimento a todos os Doentes, mas, neste caso em especial, aos Dadores Vivos de Fígado. Levo comigo, não só para a minha prática clínica, mas também para a vida, todos os ensinamentos que me deram. São, sem dúvida, um exemplo vivo de amor,

altruísmo, generosidade e coragem. Aos Dadores, porque é a eles que esta Tese se destina, a minha sincera admiração e a minha enorme gratidão.

List of Abbreviations

ASA - American Society of Anaesthesiologists

BMI - Body mass index

CPRM - Cholangio-Magnetic Resonance

Ctl - Control population

Ctl-O - Controls aged from 46 to 65 years old

Ctl-Y - Controls aged from 25 to 45 years old

EP - Emotional performance

EuraSH - Abdominal wall status inquiry

GH - General health

GI - Gastrointestinal

GIQLI - Gastrointestinal Quality of Life Index

GP – Gallbladder Polyps

IOC - Intraoperative cholangiography

IPAQ-SF - International Physical Activity Questionnaire Short-Form

IQR - Interquartile Range

LDLT - Living Donor Liver Transplantation

LLD - Liver Living Donors

LLD-O - Donors aged from 46 to 65 years old

LLD-Y - Donors aged from 25 to 45 years old

MET – Metabolic equivalent of task

MH - Mental health

P - Pain

PCS – Post-cholecystectomy syndrome

PF - Physical function

PP - Physical performance

PP - Portuguese population

QoL - Quality of life

SF - Social function

VT - Vitality/energy

Abstract

Background:

Living donor liver transplantation (LDLT) is an accepted option for patients with end-stage liver disease. However, it potentially carries the risk of donor morbi-mortality, as well as long-term functional impairment. Cholecystectomy is performed routinely in the donor intervention but the long-term effect on gastrointestinal (GI) related quality of life (QoL) has never been explored previously. This study evaluated living donors' overall, abdominal wall-related, activity-level and gastrointestinal-related QoL.

Material/Methods:

In total, 21 living liver donors (LLD) (57% females, mean age 45 ± 9 years) were compared to a control group (29 patients) undergoing cholecystectomy for gallbladder polyps (45% females, mean age 46 ± 7 years). LLD's and controls (Ctl) were divided into two age groups: LLD-Y and Ctl-Y (25-45 years); and LLD-O and Ctl-O (46-65 years). Generic SF-36, Gastrointestinal Quality of Life Index (GIQLI), EuraHS for abdominal wall status assessment and Questionnaire of Physical Activity (IPAQ) were performed. Standard age-adjusted Portuguese population (PP) SF-36 scores were used.

Results:

Global QoL results were better than PP scores and not inferior when compared to controls, scoring higher in the LLD-Y group in domains such as vitality and mental health ($p < 0.05$). The abdominal wall impact was minimal, and the activity level was significantly higher in LLD-Y than in Ctl-Y. Overall GI-related QoL was very close to the maximum score, and gastrointestinal symptoms were significantly less in LLD-O compared with Ctl-O.

Conclusion:

LDLT had no impact on donors' general, abdominal wall-related QoL or activity-level. The performance of cholecystectomy apparently had no impact on the development of GI-related symptoms.

Key-words: Liver Transplantation, Living Donor, Quality of Life, Cholecystectomy, Post-cholecystectomy syndrome

Resumo

Introdução:

O Transplante Hepático com Dador Vivo é uma solução de recurso para doentes hepáticos em estadio terminal, particularmente em idade pediátrica. No entanto, este procedimento cirúrgico pode acarretar riscos para o dador, não apenas ao nível da morbi-mortalidade, mas também relacionados com a qualidade de vida a longo prazo. Apesar do Dador ser submetido, por rotina, a uma colecistectomia durante a sua intervenção, o impacto desta na qualidade de vida gastrointestinal a longo prazo nunca foi anteriormente investigado. Este estudo procurou avaliar a qualidade de vida dos dadores a nível global, gastrointestinal, relacionada com a parede abdominal e ainda o nível de atividade física.

Materiais e Métodos:

No total, 21 dadores vivos de fígado (57% mulheres, idade média 45 ± 9) foram comparados com um grupo de controlo (Ctl) composto por 29 doentes submetidos a colecistectomia por pólipos vesiculares (45% mulheres, idade média 46 ± 7 anos). Os dadores vivos e os controlos foram divididos em dois grupos etários: LLD-Y e Ctl-Y (25-45 anos); e LLD-O e Ctl-O (46-65 anos). Foram realizados quatro questionários: SF-36 para avaliar a qualidade de vida global; *Gastrointestinal Quality of Life Index* (GIQLI); EuraHS para aferição do status da parede abdominal; e *Questionnaire of Physical Activity* (IPAQ). Foram também usados os valores standard do SF-36 para a população Portuguesa de acordo com a idade, para comparação da qualidade de vida geral dos dadores.

Resultados:

Os resultados da qualidade de vida global foram melhores que a população Portuguesa e não inferiores quando comparados com os controlos, tendo os dadores mais jovens (LLD-Y) obtido scores mais altos em domínios como vitalidade e saúde mental ($p < 0.05$). O impacto na parede abdominal foi mínimo e o nível de atividade física foi significativamente mais alto nos LLD-Y que nos Ctl-Y. A qualidade de vida gastrointestinal geral foi muito próxima do score máximo e os sintomas gastrointestinais foram significativamente inferiores nos LLD-O em comparação com os Ctl-O.

Conclusão:

O Transplante Hepático de Dador Vivo não teve impacto na qualidade de vida geral, gastrointestinal, relacionada com a parede abdominal e no nível de atividade física dos dadores. Aparentemente, a realização da colecistectomia não teve impacto no desenvolvimento de sintomas gastrointestinais.

Introduction

Living donor liver transplantation (LDLT) is an acceptable option for many patients with end-stage liver disease, particularly in paediatric age [1–4]. However, it raises significant concerns regarding possible donor morbidity and even mortality [1,2,5]. Furthermore, the donor intervention may have major impact on the donor's quality of life (QoL), not only due to decreased general health (GH) status and physical activity level, but also to non-specific gastrointestinal symptoms [6].

One possible factor is the role of routine cholecystectomy in the development of postoperative gastrointestinal symptoms [6]. This is yet mostly unexplored as it is unique to living donors of a liver graft. Due to concerns about both graft and liver remnant biliary anatomy, LDLT is frequently performed with intraoperative cholangiography (IOC) serving as a guide for the precise transection line of the biliary tree. Several alternatives for accurate operative planning are emerging, such as magnetic resonance techniques, indocyanine green fluorescence cholangiography and 3D-printed models, as well as some technical variations for IOC with gallbladder conservation [7–10]. In spite of this alternatives, cholecystectomy is routinely performed in the majority of centers performing LDLT [9,11].

Removal of a normal gallbladder can lead to profound changes in the gastrointestinal (GI) physiology. Post-cholecystectomy the bile is released continuously into the duodenum and dyspeptic symptoms, such as abdominal distention and diarrhoea, may be observed after intake of high-fat diet [6]. Additionally, cholecystectomy shortens the gut transit time by accelerating passage through the colon [12]. Patients commonly present heartburn, nausea, fatty food intolerance and general abdominal discomfort, potentially impairing daily activity. These symptoms might also be experienced by patients undergoing cholecystectomy in the absence of biliary symptoms and lithiasis, namely patients with gallbladder polyps (GP), in whom the gallbladder is removed to exclude gallbladder carcinoma.

Moreover, the LDLT operation can also cause incisional pain and herniae, aesthetic issues and other abdominal wall-related sequela that can have direct interference on daily life. Although most studies have analysed the results of LDLT in the face of postoperative morbidity and receptor outcome, there has been a shift in focus to the donors' long-term QoL. However, most studies have only looked into general QoL, which may not accurately reflect the complexity of anatomical and functional changes suffered as well as their long-term impact.

In this study, we evaluated the long-term QoL and physical activity level of a population of living donors. Specifically, we hypothesized that the cholecystectomy in LDLT is not associated with any greater impairment in GI QoL than in previously asymptomatic patients without pre-existing lithiasis undergoing cholecystectomy.

Materials and Methods

This study included two cohorts of patients: one study population and a control group. The former consisted of 21 Living Liver Donors (LLD) (57% females) who were submitted to hepatectomy for LDLT between 2001 and 2018 in *Unidade de Transplantação Hepática Pediátrica e de Adultos* of *Centro Hospitalar e Universitário de Coimbra* (Coordinator: Dr. Emanuel Furtado). The mean age of donors was 45±9 years.

In total, 29 LDLT were performed in our Center; four LLD refused to participate in our study and four were unable to contact (Figure 1A).

All donors were American Society of Anaesthesiologists (ASA) Score I or II.

All recipients were paediatric except one case – adult to adult LDLT for Familial Amyloidotic Polyneuropathy - and all donors were closely related to the recipients: 20 cases from parent to child and one uncle to niece donation.

Donor preoperative assessment included a general physical exam, comprehensive biochemical and serological screening and detailed imaging, as per institutional protocol. Angio-Computed Tomography was routinely performed, for both vascular and volumetric assessment, while Magnetic Resonance Cholangiopancreatography (MRCP) was performed selectively, particularly in cases of full-left or full-right liver grafts. All donors were assessed by an independent clinician, full consent was obtained and a formal decision by the ethics committee was required to perform the procedure.

The grafts were left lateral segment in 16 cases; full left liver grafts in four and full right liver graft in one case.

All procedures were performed by open approach, in most instances through a short upper midline laparotomy with bilateral transversal extension (inverted T).

A transcystic perioperative cholangiography was carried out in every intervention, requiring cholecystectomy. Procurement of the graft was performed as described by Darwish et al [13].

Donor morbidity was as follows: five cases of minor morbidity (Dindo-Clavien grade II - two cases of biliary fistula, two cases of ileus and one case of superficial surgical site infection); one case of major morbidity (Dindo-Clavien grade IIIb – hemoperitoneum requiring relaparotomy) [14]. There was no mortality.

Regarding the control population, in the first stage, 129 patients who underwent laparoscopic cholecystectomy between 2001 and 2018 in the Department of Surgery of *Centro Hospitalar e Universitário de Coimbra* (Head of Department: Dr. Hélder Carvalho) were selected. Indication for surgery was the ultrasonographic finding of a polyp with size greater than 10 mm and the inability to rule out gallbladder cancer. Patients with unequivocal signs of gallbladder cancer (large mass, liver parenchyma invasion, enlarged lymph nodes) were treated with upfront radical resection by laparotomy and were excluded from the study. Of the initial population, 49 patients were selected based on age (between 25 and 65 years old) and absence of three exclusion criteria: less than a year between study and the surgery, to minimize the presence of residual post-cholecystectomy symptoms; ASA class equal or higher than III; coexisting biliary lithiasis or any other known organic pathology of the digestive tract. Twenty patients refused to participate in the study (Figure 1B).

A four-port technique was used, with extraction of the specimen with the use of a retrieval bag through the infraumbilical port incision (if needed with extension of the incision to minimize risk of rupture) and immediate frozen section pathological exam. If the diagnosis of invasive carcinoma was confirmed, the procedure continued with conversion to laparotomy, resection of hepatic segments 4B and 5 and hilar lymph node dissection and these patients were excluded from the study.

The final control population consisted of 29 patients with GP (45% females), mean age 46 ± 7 years, without any preoperative symptoms. The histopathologic diagnosis were gallbladder cholesterol polyps (23 cases, 79%) and focal polypoid cholesterosis (6 cases, 21%).

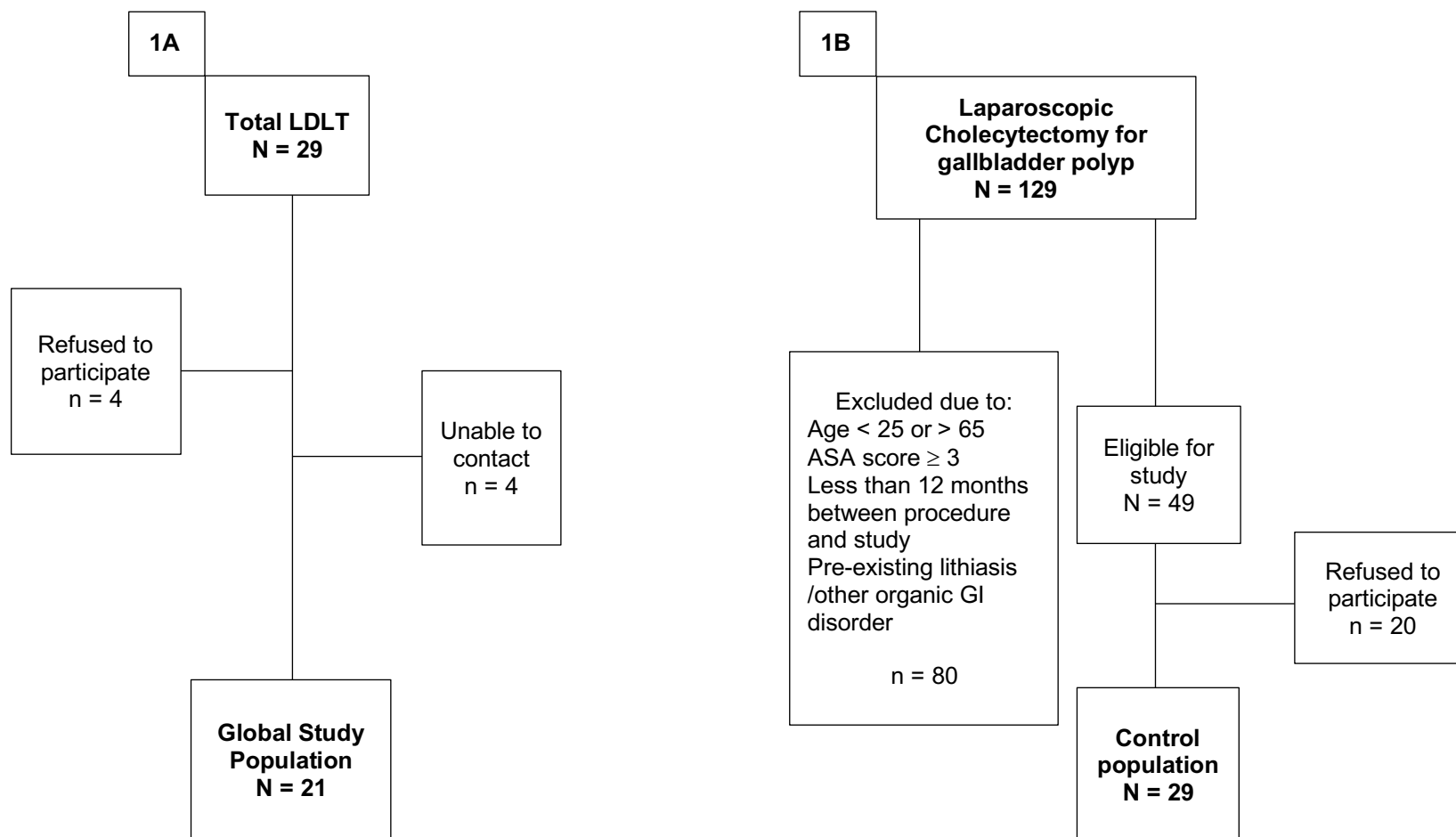


Figure 1A and B. Algorithm for global study population – Living Liver Donors from *Unidade de Transplantação Hepática Pediátrica e de Adultos* (1A) and algorithm for final control population – patients cholecystectomized for gallbladder polyps (GP) (1B), in *Centro Hospitalar e Universitário de Coimbra*.

No morbidity was reported within the control group.

In order to address the reduction of QoL with age, we divided donors (LLD) and controls (Ctl) into two age groups: a younger group (LLD-Y and Ctl-Y) from 25 to 45; and an older group (LLD-O and Ctl-O) from 46 to 65 years old - according to the age classes of the study validating the SF-36 for the Portuguese population (PP) [15,16] There were no significant differences in the distribution of gender, body mass index (BMI) and age at the time of the survey between donors and controls on both age groups (Table 1).

Both the living donors' population and the control group answered four surveys [SF-36, GIQLI (Gastrointestinal Quality of Life Index), EuraHS (Abdominal Wall evaluation) and the International Physical Activity Questionnaire Short-Form (IPAQ-SF)], in order to assess QoL and activity level. The mean time between the surgical procedures and the inquiries was, in the younger group, 106.58±72.7 months (LLD-Y) versus 53.92±12.81 months (Ctl.Y) (p=0.030); and, in the older group, 175.11±23.86 months (LLD-O) versus 56±20.70 months (Ctl-O) (p<0.001).The inquiries were performed during regular donors' postoperative follow-up and controls were asked via telephone interviews.

The SF-36 is a generic tool consisting of 36 items to assess quality of life using eight domains: physical functioning (PF); physical performance (PP); emotional performance (EP); vitality/energy (VT); pain (P); mental health (MH); social function (SF); and general health (GH). Each domain is expressed as a score from 0 to 100%; the closer to 100%, the better the QoL. SF-36 has been used in numerous other LDLT QoL studies and it has been validated for the Portuguese population (PP) [16]. Thus, we compared the median values of every SF-36 donors' domain, either in LLD-Y or LLD-O, with the same values for the PP [15].

The Gastro-intestinal Quality of Life Index (GIQLI) can be used to assess gastrointestinal-related quality of life [6]. GIQLI is a 36-item questionnaire designed to evaluate the impact of gastrointestinal symptoms and disease on daily life. The questionnaire comprises five domains: gastrointestinal (GI) symptoms (19 items); physical function (7 items); emotional function (5 items), social function (4 items); and treatment reaction (1 item). Each item is scored from 0 to 4 (0 being the worst and 4 the best condition) and the global score varies from 0 to 144. This questionnaire also allows to investigate the presence of GI complaints such as abdominal pain, eructation, retrosternal burn, increased bowel motility, diarrhea, urgency, food intolerance, vomiting and nausea, symptoms usually associated with the post-cholecystectomy syndrome

(PCS) [12,17]. The GIQLI was translated by the first author to the Portuguese language, since it had not been previously used in our country.

The abdominal wall status was evaluated by the EuraHS Questionnaire [18], a tool designed to evaluate the QoL related to inguinal hernia surgical repair and adapted for this study to evaluate the abdominal incision and performance status both in donors and in controls. Questions include: incisional pain both at rest and during mild and strenuous efforts; activity restriction due to pain or discomfort; and aesthetical results. Each item is punctuated from 0 (the best result meaning no restrictions, no pain and highly satisfactory cosmetic result) to 10 (the worse result).

Physical activity level was measured according to IPAQ-SF [19], a tool designed in the first instance for population surveillance of physical activity among adults that became a commonly used in many surgical patients [20]. Three specific types of activities were monitored: walking, moderate-intensity and vigorous-intensity activities. The IPAQ-SF provides separate scores on the three specific activities mentioned above and the sum of each results in the total score of physical activity measured in Metabolic Equivalent of Task (METs)/week. This instrument also classifies physical activity according to a categorical score: low, moderate and high levels of activity. This survey has also been validated for the PP [21].

Table 1. Study population and control group characteristics - Comparison between study population of 21 liver living donors (LLD) and control group of 29 patients undergoing laparoscopic cholecystectomy for gallbladder polyps (Ctl), divided in two age groups (25-45) (Y) and (46-65) (O). Shapiro-Wilk test for normal distribution and comparison of variables using *t* test (*) form normal continuous distribution and Mann-Whitney for non-normal distribution (p<0.05). Nominal variables compared with X² test.

	[25-45] years			[46-65] years		
	Ctl-Y (n=12)	LLD-Y (n=12)	p-value	Ctl-O (n=17)	LLD-O (n=9)	p-value
Sex (male/female)	7/5	6/6	0.682	6/11	2/7	0.492
Age at the time of the survey	42; IQR = 6	41; IQR = 9	0.478	51, IQR = 6	53; IQR =9	0.148
BMI (Kg/m ²) (*)	25.97 ± 4.73	23.85 ± 3.14	0.209	27.76 ± 5.84	25.34 ± 3.40	0.195
Length of Stay (days)	4; IQR = 2	8; IQR = 4	< 0.001	4; IQR = 2	7; IQR = 3	< 0.001
Morbidity	0	5	0.005	0	1	0.161
Major Morbidity	0	1	0.161	0	0	1
Minor Morbidity	0	4	0.028	0	1	0.307
Co-morbidities						
Arterial Hypertension	4	0	0.028	2	2	0.482
Diabetes Mellitus	0	0	1	1	0	0.458
Peripheral Venous Disease	1	0	0.307	3	0	0.180
Dyslipidemia	0	1	0.307	3	1	0.660
Depression	1	0	0.307	4	0	0.114
Osteoarticular Disease	1	0	0.307	7	0	0.024
Coronary Disease	1	0	0.307	4	0	0.114
Respiratory Tract Disease	5	0	0.012	1	0	0.458

IQR – interquartile range

The study protocol was approved by the *Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra* in 2017 and both patients and controls gave their informed consent for participation in the study. All data collected was maintained under anonymity and all the rights established by the Declarations of Helsinki were guaranteed.

Data was analysed with SPSS™ (version 25.0 for Windows). Shapiro-Wilk test for normality assessment. Nominal variables compared with X^2 test. T test for continuous samples with normal distribution, if not Mann-Whitney test, p-value <0.05.

Results

Global Quality of Life (SF-36)

When comparing the donor SF-36 values with the standard values for the PP divided in the same age groups, both groups (LLD-Y and LLD-O) presented better results ($p < 0.05$) in all SF-36 domains except emotional performance (EP) domain, where no significant differences were found, neither in LLD-Y nor LLD-O ($p > 0.05$) (Table 2).

Both SF-36 domains were compared between living donors (LLD-Y and LLD-O) and controls (Ctl-Y and Ctl-O) (Figures 2 and 3, and Table 3). In LLD-Y, donors presented higher SF-36 median scores than the control group in domains such as vitality/energy (VT) ($p = 0.002$) and mental health (MH) ($p = 0.020$). All other SF-36 domains presented no difference between these two groups. In LLD-O, there was no difference in QoL scores between groups.

Neither comorbidities nor postoperative morbidity were associated with decreased overall long-term QoL assessed with SF-36 ($p > 0.05$).

Table 2. Quality of life in Living donors and Portuguese population. Results of health-related quality of life using overall SF-36 and individual domains in 21 liver living donor (LLD) and baseline results from the Portuguese population, according to [15], divided into age groups (SF-36 domains' median values). Mann-Whitney test ($p < 0.05$).

SF-36 Domains	[25-45] years					[46-65] years				
	Portuguese Population (N=1313)		Donors LLD-Y (n=12)		p-value	Portuguese Population (N=584)		Donors LLD-O (n=9)		p-value
	Median	IQR	Median	IQR		Median	IQR	Median	IQR	
Physical Function (PF)	87.5	40	100	5	0.011	71.24	39.4	100	2.5	0.005
Physical Performance (PP)	78.15	43.7	100	0	0.001	62.5	40.15	100	0	0.003
Emotional Performance (EP)	79.15	41.7	100	0	0.179	70.85	41.65	100	0	0.083
Vitality/Energy (VT)	57.5	35	92.5	18.75	0.002	52.5	32.5	70	32.5	0.002
Mental Health (MH)	68	34	97.5	16	0.003	62	32.25	88	22	0.013
Social Functioning (SF)	81.25	37.5	100	9.38	0.004	71.9	37.5	100	0	0.004
Pain (P)	62	32.6	95	30	0.004	57	30.35	100	0	0.003
General Health (GH)	56	24.5	87.5	22.5	0.003	48.5	26	85	12.5	0.007

IQR = interquartile range

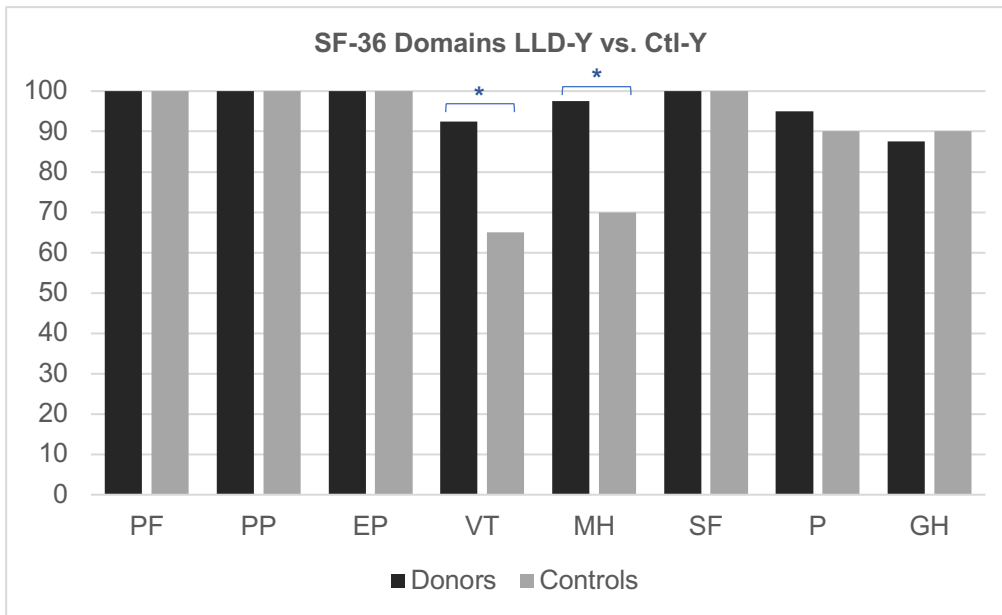


Figure 2. Comparison of every SF-36 domain between Living Liver Donors aged from 25 to 45 years (LLD-Y) (n=12) and control population of patients cholecystectomized for gallbladder polyps aged from 25 to 45 years (Ctl-Y) (n=12). Mann-Whitney test. * - $p < 0.05$. PF (physical function); PP (physical performance); EP (emotional performance); VT (vitality/energy); MH (mental health); SF (social function); P (pain); GH (general health).

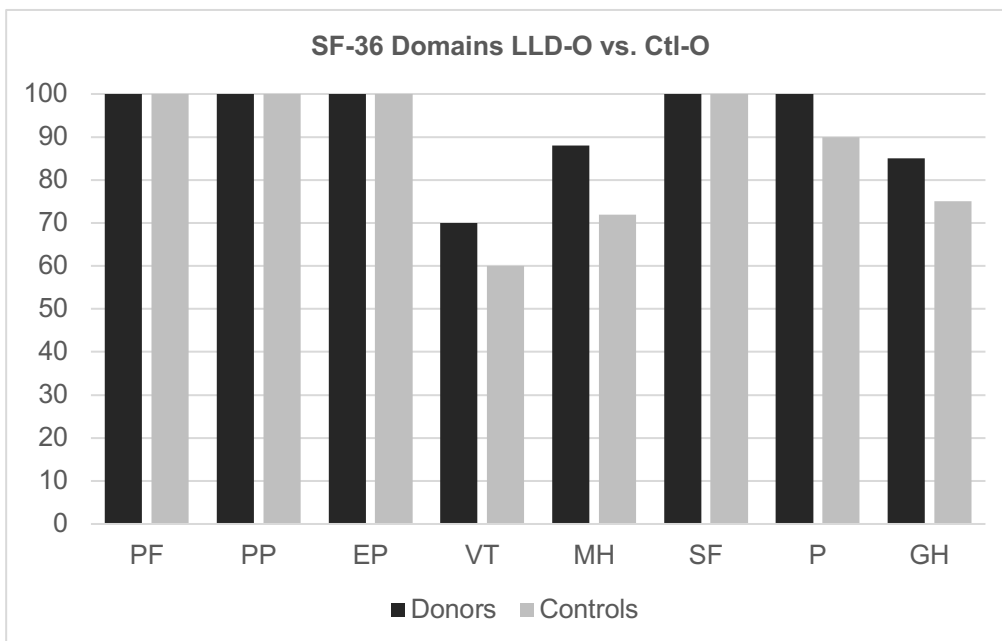


Figure 3. Comparison of every SF-36 domain between Living Liver Donors aged from 46 to 65 years (LLD-O) (n=9) and control population of patients cholecystectomized for gallbladder polyps aged from 46 to 65 years (Ctl-O) (n=17). Mann-Whitney test ($p < 0.05$). PF (physical function); PP (physical performance); EP (emotional performance); VT (vitality/energy); MH (mental health); SF (social function); P (pain); GH (general health).

Table 3. Quality of life in Living donors and controls undergoing cholecystectomy. Results of health-related quality of life using overall and individual SF-36 domains in 21 liver living donor (LLD) and 29 control patients (Ctl) undergoing cholecystectomy for gallbladder polyps, divided into age groups (SF-36 domains' median values). Mann-Whitney test, $p < 0.05$.

SF-36 Domains	[25-45] years					[46-65] years				
	Ctl-Y (n=12)		LLD-Y (n=12)		p-value	Ctl-O (n=17)		LLD-O (n=9)		p-value
	Median	IQR	Median	IQR		Median	IQR	Median	IQR	
Physical Function (PF)	100	0	100	5	0.178	100	7.5	100	2.5	0.634
Physical Performance (PP)	100	0	100	0	0.514	100	0	100	0	1.000
Emotional Performance (EP)	100	0	100	0	0.713	100	0	100	0	0.833
Vitality/Energy (VT)	65	16.25	92.5	18.75	0.002	60	22.5	70	32.5	0.200
Mental Health (MH)	70	40	97.5	16	0.020	72	38	88	22	0.220
Social Functioning (SF)	100	18.75	100	9.38	0.843	100	25	100	0	0.312
Pain (P)	90	28.75	95	30	0.977	90	32.5	100	0	0.051
General Health (GH)	90	15	87.5	22.5	0.630	75	37.50	85	12.5	0.148

IQR = interquartile range

Gastrointestinal Quality of Life (GIQLI)

There was no significant difference in GIQLI scores between LLD-Y (median value of 130) and Ctl-Y (median value of 134) (Mann-Whitney test, $p>0.05$). On the other hand, there was a significant intergroup difference in the older groups (LLD-O and Ctl-O median value of 130 and 116, respectively, $p=0.021$) (Table 4).

Regarding individual GIQLI questions on symptoms commonly associated with post-cholecystectomy syndrome (PCS), no significant difference on GI symptoms was found after comparing the younger groups. However, the LLD-O group presented significantly less GI complaints than the Ctl-O group, particularly abdominal pain, eructation, diarrhea, vomiting, nausea and retrosternal burn ($p<0.05$) (Table 4).

Table 4. Gastrointestinal health-related quality of life in living donors and controls. Gastrointestinal Quality of Life Index (GIQLI) general score (0-144 maximum) and specific questions related to the post-cholecystectomy syndrome (0-4 maximum score per question) in 21 liver living donors (LLD) and 29 control patients (Ctl) undergoing cholecystectomy for gallbladder polyps, according to age groups. Data presented as mean \pm standard error. T test for two independent samples, $p < 0.05$.

		[25-45] years			[46-65] years		
		Ctl-Y (n=12)	LLD-Y (n=12)	p-value	Ctl-O (n=17)	LLD-O (n=9)	p-value
GIQLI		134 \pm 5	130 \pm 10	0.174	116 \pm 19	130 \pm 9	0.021
GIQLI – particular questions	Abdominal pain	3.769 \pm 0.58	3.67 \pm 0.89	0.685	3.27 \pm 0.97	4	0.005
	Eructation	3.21 \pm 1.19	3.75 \pm 0.62	0.173	2.82 \pm 1.33	3.78 \pm 0.44	0.014
	Increased bowel motility	3.71 \pm 1.07	3.58 \pm 0.79	0.730	3.82 \pm 0.73	3.89 \pm 0.33	0.802
	Food restrictions	3.07 \pm 1.27	3.58 \pm 0.79	0.239	3.12 \pm 1.27	3.78 \pm 0.67	0.095
	Regurgitation	3.50 \pm 0.65	3.75 \pm 0.62	0.239	2.82 \pm 1.59	3.78 \pm 0.67	0.043
	Urgency	3.64 \pm 1.08	3.92 \pm 0.29	0.404	3.59 \pm 0.62	3.89 \pm 0.33	0.120
	Diarrhea	3.43 \pm 0.94	3.58 \pm 0.80	0.657	3.41 \pm 0.80	4	0.008
	Vomits or nauseas	3.64 \pm 0.75	3.67 \pm 0.65	0.932	3.35 \pm 1.00	4	0.017
	Retrosternal burn	3.00 \pm 1.36	3.58 \pm 0.67	0.172	1.41 \pm 1.70	3.78 \pm 0.67	0.008

Abdominal wall-related Quality of Life (EuraHS) and Physical Activity Level (IPAQ)

Overall, there was no impact on abdominal wall-related QoL in control patients, all submitted to a laparoscopic procedure.

In the LLD groups, there was minor impact on abdominal wall-related incisional pain and daily life restrictions, as assessed by the EuraHS score (all mean values 1.33 or under, on a scale of 0 [the best] to 10 [the worst]). These scores were not statistically different when compared to the controls. However, aesthetic dissatisfaction related to the shape of the abdomen was significantly higher in LLD-O (Table 5).

Only one case of incisional hernia in the donors' group (LLD-O), was found and corrected without any complications (the inquiry was performed before the surgical correction procedure).

In LLD-Y, donors presented a higher physical activity level (1090 ± 875 METs/week) than the Ctl-Y (225 ± 429 METs/week), as assessed by the IPAQ, ($p=0.006$). These differences were not statistically significant in the older groups (LLD-O and Ctl-O), 1137 ± 889 METs/week vs 648 ± 706 METs/week, respectively ($p = 0.148$).

Table 5. Abdominal wall-related quality of life in living donors and controls. EuraHS questionnaire individual scores (0 [the best] to 10 [the worst] points), in 21 liver living donors (LLD) and 29 control patients (Ctl) undergoing cholecystectomy for gallbladder polyps, according to age groups. Data presented as mean \pm standard error. T test for two independent samples, $p < 0.05$.

	[25-45] years			[46-65] years		
	Ctl-Y (n=12)	LLD-Y (n=12)	p-value	Ctl-O (n=17)	LLD-O (n=9)	p-value
Incisional pain						
At rest	0	0.25 \pm 0.87	0.328	0.24 \pm 0.97	0	0.332
During daily activities	0	0.08 \pm 0.28	0.328	0.12 \pm 0.49	0.78 \pm 2.33	0.256
In the last week	0	0.42 \pm 1.17	0.241	0	0	0.347
Restrictions						
During daily life	0	0	0.339	0	0	0.347
Outdoor activities	0	0.25 \pm 0.87	0.328	0	0.22 \pm 0.67	0.347
During sports practicing	0	0.08 \pm 0.28	0.328	0	0.22 \pm 0.67	0.174
For strenuous efforts	0	0.67 \pm 1.37	0.106	0	1.33 \pm 3.31	0.104
Aesthetic result						
Abdominal shape	0.58 \pm 2.02	2.33 \pm 3.40	0.139	0	3 \pm 3.80	0.003
Incisional scar	0.58 \pm 2.02	2.17 \pm 3.40	0.180	0	1.22 \pm 1.97	0.102

Discussion

Living Donor Liver Transplantation is an accepted option for terminal liver disease, particularly in paediatric cases, with unquestionable advantages for the recipients. Even though the surgical team's major concern is on donors' safety, minimizing postoperative mortality and morbidity, the long-term impact on QoL must also be considered.

Many centers have been investigating the psychological and physical impact [20] of this procedure including long-term QoL in general, using the SF-36 - a worldwide-validated inquiry. Moreover, most studies focus only on the living donors alone, without comparing them with a control population of healthy people. Living donors are previously healthy and productive young adults who are submitted to a major surgical procedure of which they do not derive any direct benefit. Thus, a mere description of overall short-term outcomes, meaning morbidity and mortality, although important, is obviously insufficient. It is of the utmost importance to compare their long-term outcomes, not only with other patients who underwent an abdominal surgical procedure, but specially with previously healthy, asymptomatic people.

Based on the above assumptions, we decided to compare our living liver donors (LLD) population with two control populations: the Portuguese population and a population of patients who underwent cholecystectomy for gallbladder polyps (GB).

The reasons for the choice of this aforementioned control group are multifactorial. Most liver resections are performed for malignant disease, some requiring cholecystectomy. Selecting a control group of patients undergoing hepatic resection would be extremely difficult as these patients are distinct in many ways to the young, healthy and highly selected living liver donor. Patients undergoing hepatectomy have often undergone chemotherapy, might have previous abdominal incisions and could present GI symptoms and / or pathology. Thus, their vitality, emotional and physical functions may present significant impairment. As our main objective was to investigate, not only general QoL, but also the impact of cholecystectomy, we considered patients with GP [22], a group in many ways comparable with LLD, despite the notable difference that they were all approached laparoscopically.

Our results confirm that donors in both age groups have, apparently, better overall QoL (SF-36 scores) than the Portuguese population, except on emotional performance

domain. Obviously, there may exist a bias because age was the only matched characteristic between donors and the PP, whereas variables such as BMI or comorbidities were unknown.

When compared to the GP controls, and despite the use of laparotomy, SF-36 results of our donor population are not inferior to these controls, scoring higher in the LLD-Y group in domains like vitality/energy (VT) and mental health (MH). However, we admit two unequivocal biases in the present study. Firstly, the time between surgery and the surveys is significantly different between donors and controls. On the other hand, the donors' SF-36 scores were not assessed preoperatively. This may be explained by the long study period, starting at a time when QoL was not as highly valued in the LDLT context as it is nowadays.

Another key issue is the fact that, in our study, donors, are overwhelmingly parents of children with end-stage liver disease. Thus, they might experience a gain in QoL by the improvement in their offspring's general health condition. To what level would this increase in general QoL contribute to our findings is, after all, unknown. Nonetheless, although this might contribute to an improvement in general QoL, it would likely not cause such a significant effect in GI-related QoL, an issue that has never been addressed in previous studies. In fact, since the SF-36 only measures general QoL, it may not reflect the true effect of cholecystectomy on previously healthy donors. To the best of our knowledge, this has never been clearly addressed in the setting of LDLT and motivated our study.

The division of the biliary tract, ensuring that both graft and donor remnant liver preserve a fully functional biliary tract with unjeopardized vascularization, is a key point during the liver living donor operation [8]. During the procedure, in order to avoid biliary tract lesions, we, as in most centers, perform a transcystic cholangiography, invariably requiring a cholecystectomy [23].

As reported in the literature [24–26], biliary anatomical variations can be both frequent and complex, and despite the preoperative use of MRCP in some centers, a precise transection of the bile duct is required to ensure safety [24,26]. Some groups avoid doing a routine cholecystectomy during LDLT, reporting good results. Wei et al. resort to MRCP in the preoperative period and also intra-operative cholangiography through the stump of the segment 4 biliary duct [27] in left liver lateral segment grafts. Still, others use contrast enhanced intraoperative ultrasonic cholangiography, confirming the feasibility and safety of preserving the gallbladder [11]. In order to avoid cholecystectomy, some

authors even perform direct catheter puncture of the common bile duct for IOC, suture closing the puncture site with 6-0 polypropylene [28]. Despite being very attractive, these procedures are technically difficult during a surgical intervention that, in its essence, must be kept as simple as possible. In addition, to the best of our knowledge, there are no guarantees on the normal functioning of a gallbladder that has been partially dissected from its bed, as is required to obtain a full-right or a full-left liver graft [29].

As such, cholecystectomy is still the modality of choice in most centers performing LDLT but can potentially cause significant physiologic changes. After removal of the gallbladder, the bile is released continuously into the intestinal tract and dyspeptic symptoms can occur causing PCS, also related to sphincter of Oddi's dysfunction [30]. Cholecystectomy can also increase the risk of colon cancer, not only due to the generation of secondary cholic acid – that may increase mitotic and mutational rates of colonic mucosal cells - but also because of changes in gut microbiome [31,32].

The impact on GI QoL is an innovative aspect of our study as it is the first time the GIQLI score is used in living donors to specifically address the effect of cholecystectomy. In fact, the GIQLI scores were very high and close to the maximum score, either globally (maximum score of 144) or when analyzing individual GI symptoms related to PCS (maximum individual score of 4 per symptom). This is particularly more relevant in the LLD-O donors, whose GI individual QoL scores are significantly better than the controls'. Admittedly, we came across the same problem as we did with the SF-36, as there is no baseline pre-donation value. However, this can be easily explained by the fact that only until recently there were no tools to assess GI QoL such as the GIQLI survey. Another limitation of our study is that there is no standard baseline value for a healthy population, nor is GIQLI validated for the Portuguese population. In spite of these caveats, we can confirm that cholecystectomy in LDLT apparently does not present a negative impact on GI QoL.

As expected, the impact on abdominal wall QoL was worse among LLD's but, surprisingly, only on the aesthetic outcome in the older cohort of donors. We acknowledge that this surgical intervention has been increasingly performed by laparoscopic approach but more evidence is needed [33]. As a matter of fact, our results do not reflect the advantages of this minimal invasive technique such as: earlier return to active life, decreased postoperative pain, better postoperative recovery and improved aesthetic results. These issues are very important but were not the aim of our study. What is important to retain, possibly more than the abdominal wall QoL, is the physical

activity level. This parameter was particularly higher in the LLD-Y donors when compared to Ctl-Y, whose abdominal wall muscle integrity, of the utmost importance for physical exercise of any kind, was preserved by the less invasive approach. Nonetheless, we must look at these results with due reserve in the light that the population of donors in our center is highly motivated (all except one were parents to the recipient), and this may bias the responses in one of the most subjective surveys that we performed, the EuraHS. This could explain the apparently low impact on abdominal wall-related QoL.

Finally, apart from the already discussed limitations of our study (long study period, lack of preoperative assessment of QoL) we must acknowledge another one, which is related to the very particular personality traits of living donors. Their altruistic and relatively stoic nature might influence the way they perceive the impact of the changes brought about by the donor operation. Nonetheless, when studying the subjective nature of health-related quality of life, the physician is indeed trying to ascertain, by definition, the impact perceived by the patient.

Ever since, surgery has always been used to treat life-threatening disorders, such as trauma and neoplasms. Thus, surgeons' main priorities have been to ensure immediate outcomes such as mortality and morbidity, while enhancing overall and disease-free survival. The paradigm of surgical reality is changing, bringing to discussion issues such as patients' QoL and long-term functional impairment, which should also be considered endpoints of any surgical procedure [34].

While studying QoL, we are obliged to reflect on our actions as surgeons and, therefore, to seriously reconsider the real benefit and the potential harm that a given surgical procedure might have on a given individual.

As such, in our center we are prospectively evaluating the quality of life of future living donors using the same surveys used in this study in order to properly assess both pre and postdonation status. Also, we strongly advise all centers performing LDLT to use some measure of QoL as metric of donor outcome, in order to fully ascertain the long-term impact on these previously healthy young adults. This will be an unavoidable contribution to the debate surrounding the use of living donors in liver transplantation.

Conclusion

In conclusion, LDLT has apparently no impact on donors' global, GI and abdominal wall long-term QoL. Despite the advantages of laparoscopy, in our study the laparotomic approach apparently did not compromise the donors' long-term abdominal wall performance status or activity level. Additionally, cholecystectomy is apparently not harmful to the donors and combined with IOC is still an acceptable technique to guarantee biliary tract safety for both donor and recipient. We strongly advise all centers performing LDLT to assess donors' QoL, in the preoperative and postoperative setting. In the authors' opinion, QoL should be regarded as metric of donor outcome, so that the true perceived impact of this procedure may be ascertained.

References

- [1] Xu D, Long X, Xia Q. A review of life quality in living donors after liver transplantation. *Int J Clin Exp Med* 2015;8:20–6.
- [2] Kawagishi N, Takeda I, Miyagi S, Sato K, Ohuchi N. Donors' quality of life evaluated by short form-36 analysis after living donor liver transplantation in a single-center experience. *Transplant Proc* 2014;46:675–7.
- [3] Shoji M, Ohkohchi N, Fujimori K, Koyamada N, Sekiguchi S, Kawagishi N, et al. The safety of the donor operation in living-donor liver transplantation: An analysis of 45 donors. *Transpl Int* 2003;16:461–4.
- [4] Dew MA, Butt Z, Humar A, DiMartini AF. Long-Term Medical and Psychosocial Outcomes in Living Liver Donors. *Am J Transplant* 2017;17:880–92.
- [5] Miyagi S, Kawagishi N, Fujimori K, Sekiguchi S, Fukumori T, Akamatsu Y, et al. Risks of donation and quality of donors' life after living donor liver transplantation. *Transpl Int* 2005;18:47–51.
- [6] Wang SH, Ming YZ, Lin PY, Wang JY, Lin HC, Hsieh CE, et al. Predictors of diarrhea after hepatectomy and its impact on gastrointestinal quality of life in living donors. *PLoS One* 2016;11:4–11.
- [7] Soejima Y, Taguchi T, Sugimoto M, Hayashida M, Yoshizumi T, Ikegami T, et al. Three-dimensional printing and biotexture modeling for preoperative simulation in living donor liver transplantation for small infants. *Liver Transplant* 2016;22:1610–4.
- [8] Javan R, Zeman MN. A Prototype Educational Model for Hepatobiliary Interventions: Unveiling the Role of Graphic Designers in Medical 3D Printing. *J Digit Imaging* 2017:1–11.
- [9] Urade T, Fukumoto T, Kido M, Takebe A, Tanaka M, Kuramitsu K, et al. Contrast-enhanced intraoperative ultrasonic cholangiography in living donor hepatectomy. *Liver Transplant* 2016;22:1437–42.
- [10] Mizuno S, Isaji S. Indocyanine green (ICG) fluorescence imaging-guided cholangiography for donor hepatectomy in living donor liver transplantation. *Am J Transplant* 2010;10:2725–6.
- [11] Dong JH, Ye S, Duan WD, Ji WB, Liang YR. Feasibility of liver graft procurement with donor gallbladder preservation in living donor liver transplantation. *Hepatol Int* 2015;9:603–11.
- [12] Fort JM, Azpiroz F, Casellas F, Andreu J, Malagelada JR. Bowel habit after cholecystectomy: Physiological changes and clinical implications. *Gastroenterology* 1996;111:617–22.

- [13] Darwish AA, Bourdeaux C, Kader HA, Janssen M, Sokal E, Lerut J, et al. Pediatric liver transplantation using left hepatic segments from living related donors: Surgical experience in 100 recipients at Saint-Luc University Clinics. *Pediatr Transplant* 2006;10:345–53.
- [14] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
- [15] Lopes P, Noronha L, Nobre L. Artigo original Medidas sumário física e mental de estado de saúde para a população portuguesa. *Rev Port Saúde Pública* 2012;0:163–71.
- [16] Ferreira PL, Santana P. Percepção de estado de saúde e de qualidade de vida da população activa: contributo para a definição de normas portuguesas. *Rev Port Saúde Pública* 2003;21:15–30.
- [17] L M, Z D, A S. Postcholecystectomy Syndrome: From Pathophysiology to Differential Diagnosis - A Critical Review. *Pancreat Disord Ther* 2015;05.
- [18] Muysoms F, Campanelli G, Champault GG, DeBeaux AC, Dietz UA, Jeekel J, et al. EuraHS: The Development of an international online platform for registration and outcome measurement of ventral abdominal wall Hernia repair. *Hernia* 2012;16:239–50.
- [19] Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-Country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381–95.
- [20] Janik MK, Książopolska A, Kostrzewa K, Kobryń K, Moskwa M, Raszeja-Wyszomirska J, et al. Long-Term Health-Related Quality of Life in Living Liver Donors. *Ann Transplant* 2019;24:45–51.
- [21] Luís D, Bettencourt F, Júri S, Presidente :, Doutora P, Helena M, et al. VALIDADE SIMULTÂNEA DO QUESTIONÁRIO INTERNACIONAL DE ACTIVIDADE FÍSICA ATRAVÉS DA MEDIÇÃO OBJECTIVA DA ACTIVIDADE FÍSICA POR ACTIGRAFIA PROPORCIONAL Dissertação elaborada com vista à obtenção do Grau de Mestre em Exercício e Saúde 2016.
- [22] Wiles R, Thoeni RF, Barbu ST, Vashist YK, Rafaelsen SR, Dewhurst C, et al. Management and follow-up of gallbladder polyps: Joint guidelines between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Societ. *Eur Radiol* 2017;27:3856–66.
- [23] Ohkubo M, Nagino M, Kamiya J, Yuasa N, Oda K, Arai T, et al. Surgical Anatomy of the Bile Ducts at the Hepatic Hilum as Applied to Living Donor Liver

- Transplantation. *Ann Surg* 2004;239:82–6.
- [24] Deka P, Islam M, Jindal D, Kumar N, Arora A, Negi SS. An analysis of biliary anatomy according to different classification systems. *Indian J Gastroenterol* 2014;33:23–30.
- [25] Pessanha I, Alexandrino H, Piedade C, Cunha C, Gonçalves I, Lopes MF, et al. Successful liver transplantation using a whole liver graft with gallbladder agenesis: First report in pediatric liver transplantation. *Pediatr Transplant* 2019;23.
- [26] Choi JW, Kim TK, Kim KW, Kim AY, Kim PN, Ha HK, et al. Anatomic variation in intrahepatic bile ducts: An analysis of intraoperative cholangiograms in 300 consecutive donors for living donor liver transplantation. *Korean J Radiol* 2003;4:85–90.
- [27] Wei L, Zhang ZT, Zhu ZJ, Sun LY, Zeng ZG, Qu W, et al. A New Approach to Accomplish Intraoperative Cholangiography in Left Lateral Segmentectomy of Living Liver Donation. *Ann Transplant* 2019;24:155–61.
- [28] Tanaka K, Inomata Y, Kaihara S. Living-donor liver transplantation, Surgical techniques and innovations. 2003.
- [29] Gao F, Xu X, Zhu YB, Wei Q, Zhou B, Shen XY, et al. Impact of intra-operative cholangiography and parenchymal resection to donor liver function in living donor liver transplantation. *Hepatobiliary Pancreat Dis Int* 2014;13:259–63.
- [30] Behar J. Physiology and Pathophysiology of the Biliary Tract: The Gallbladder and Sphincter of Oddi—A Review. *ISRN Physiol* 2013;2013:1–15.
- [31] Wang W, Wang J, Li J, Yan P, Jin Y, Zhang R, et al. Cholecystectomy damages aging-associated intestinal microbiota construction. *Front Microbiol* 2018;9:1–9.
- [32] Hearing SD, Thomas LA, Heaton KW, Hunt L. Effect of cholecystectomy on bowel function: A prospective, controlled study. *Gut* 1999;45:889–94.
- [33] Han HS, Cho JY, Kaneko H, Wakabayashi G, Okajima H, Uemoto S, et al. Expert Panel Statement on Laparoscopic Living Donor Hepatectomy. *Dig Surg* 2018;35:284–8.
- [34] Alexandrino H. From the editor's desk - Quality in surgery: From quality of care to quality of life | From the editor's desk - Qualidade na cirurgia: Da qualidade do cuidado à qualidade de vida. *Acta Med Port* 2018;31:366–7.

Outros trabalhos / Apresentações

Ao longo do desenvolvimento da presente Tese foram sendo apresentados diversos trabalhos, que serão infra expostos.

Apresentações em Reuniões de Serviço:

“Transplante Hepático com Dador Vivo. Ficarão os Dadores Vivos realmente doentes depois da cirurgia? Qualidade de Vida a Longo Prazo”, Maria João Cardoso. Reunião de Hepatologia Pediátrica da Unidade de Transplantação Hepática Pediátrica e de Adultos do Centro Hospitalar e Universitário de Coimbra a 27/2/2019.

Apresentações em Congressos e Reuniões Nacionais:

“*Living Donor Liver Transplant – Do donors really become sick after surgery?*” Maria João Cardoso, Henrique Alexandrino, Pedro Oliveira, Ana Sofia Oliveira, Vera Vieira, Ricardo Martins, Dulce Diogo, Maria Francelina Lopes, Carlos Bento, Emanuel Furtado. In4med, Congresso Organizado pelo Núcleo de Estudantes de Medicina da Universidade de Coimbra. Coimbra 21 a 25/2/2019 – Comunicação Poster

“O Dador Vivo de Fígado ficará mesmo doente? Resultados a longo prazo da qualidade de Vida”, Maria João Cardoso, Henrique Alexandrino, Pedro Oliveira, Ana Sofia Oliveira, Vera Vieira, Ricardo Martins, Dulce Diogo, Maria Francelina Lopes, Carlos Bento, Emanuel Furtado.

XXXIX Congresso Nacional de Cirurgia, Tomar, 21 a 23/3/2019 – Comunicação Oral

“Qualidade de Vida após Doação de Fígado. Os Dadores Vivos são saudáveis até à cirurgia. E depois dela?”, Maria João Cardoso, Henrique Alexandrino, Pedro Oliveira, Ana Sofia Oliveira, Vera Vieira, Ricardo Martins, Dulce Diogo, Maria Francelina Lopes, Carlos Bento, Emanuel Furtado.

Congresso Nacional de Hepatologia, Xª Reunião da Associação Portuguesa de Estudo do Fígado. Figueira da Foz, 29 e 30/03/2019 – Comunicação Oral

Apresentações em Congressos e Reuniões Internacionais:

“*Living Donor Liver Transplant – Do donors really become sick after surgery?*”, Maria João Cardoso, Henrique Alexandrino, Pedro Oliveira, Ana Sofia Oliveira, Luís Ferreira,

Vera Vieira, Ricardo Martins, Dulce Diogo, Maria Francelina Lopes, Carlos Bento, Emanuel Furtado.

Congresso da *European-African Hepato-Pancreato-Biliary Association (E-AHPBA)* 2019. Amesterdão, 2/06/2019 – Comunicação Poster

Resumos publicados:

Cardoso MJ, Alexandrino H, Oliveira P, Oliveira, A, Vieira V, Martins R, Diogo D, Lopes F, Bento C, Furtado E: “O Dador Vivo de Fígado ficará mesmo doente – Resultados a longo prazo da qualidade de vida”. *Revista Portuguesa de Cirurgia*, suplemento de Março de 2019.

Artigo submetido em Revista Indexada:

Madeira-Cardoso MJ, Alexandrino H, Oliveira P, Rodrigues F, Oliveira A, Vieira V, Oliveiros B, Tralhão G, Carvalho H, Furtado E: “*Is Cholecystectomy really harmful? – a Long-Term Quality of Life Study in Living Donor Liver Transplantation*”. *Transplantation Proceedings*, (submetido) September 2019.