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# Clinical evaluation of pharmacists' interventions on multidisciplinary lung transplant outpatients' management: results of a 7-year observational study

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# TITLE PAGE

**Title:** Clinical evaluation of pharmacists' interventions on multidisciplinary lung transplant outpatients' management: results of a 7-year observational study

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## ABSTRACT

Objectives: Lung transplant (LT) recipients require multidisciplinary care because of the complexity of therapeutic management. Pharmacists are able to detect drug related problems and provide recommendations to physicians through pharmacists' interventions (PIs). We aimed at assessing the clinical impact of PIs on therapeutic management in LT outpatients.

Design: Data collected through a prospective cohort study during 7 years. A multidisciplinary committee assessed retrospectively the clinical impact of accepted PIs.

Setting: French University Hospital.

Participants: LT outpatients followed from 2009 to 2015.

Primary outcome measures: Clinical impact of PIs performed by pharmacists using the CLEO© tool and the Pareto chart.

Results: 1,449 PIs led to a change in patient therapeutic management and were mainly related to wrong dosage (39.6%) and untreated indication (19.6%). The clinical impact of PIs was lethal, major and moderate in 0.1%, 7.0%, and 57.9%, respectively. Immunosuppressants, antimycotics for systemic use, and antithrombotic agents had the greatest clinical impact according to the Pareto chart. PIs related to drug-drug interactions (10%) mainly had a moderate and major clinical impact (82.3%).

Conclusion: Clinical pharmacists play a key role for optimizing therapeutic management in LT outpatients. Our study provides a new insight to analyze the clinical impact of pharmacist's intervention in order to optimize clinical practice.




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## Article Summary

- Pharmacist's clinical impact is assessed through a new validated scale and analysed according to Pareto principle
- Pharmacist's added value is underlined through a collaborative practice model in lung transplantation over a 7-year period
- Clinical pharmacists' key role is highlighted for optimizing therapeutic management in lung transplant outpatients
- This retrospective single center study was performed over a 7 year-period

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## MAIN TEXT

## 1. Introduction

Lung transplantation is an established treatment for patients with end-stage lung disease. Lung transplant (LT) recipients require multidisciplinary care because of the complexity of long-term immunosuppressive therapy and other specific therapies with narrow therapeutic index, leading to potential severe adverse drug events and drug-drug interactions[1–3]. Involving pharmacists in a multidisciplinary transplant care teams may improve medication use[4] and some studies have highlighted the positive impact of the clinical pharmacist's involvement in solid organ transplantation since 1976[5,6]. Transplant pharmacists may reduce medication errors, improve patient's education and his drug knowledge as well as detect drug related problems (DRPs)[7–10] ; they decrease the average hospital length of stay[11] and improve transplant recipients medication's adherence by providing intensified pharmaceutical care during the first post-transplant year[12]. Clinical pharmacist is also an essential member of the transplant team for the prevention and treatment of transplant infectious diseases[13], and for managing tacrolimus dosage[14]. However, pharmaceutical care in LT recipients is less studied than in renal or liver transplantation and the impact of clinical pharmacists' interventions (PIs) is poorly studied in lung transplantation.

A Pharmacist Collaborative Care Program (PCCP) has been initiated in the lung transplantation center of Grenoble University Hospital (France) since 2008. There is no current accreditation for transplant pharmacist in our country but our lung transplantation center is approved by the *French Biomedicine Agency* and involves pharmacists as experts in drug therapy[15]. This program includes patient interviews and



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medication review during which pharmacists can detect DRPs and transmit PIs to physicians. DRP is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes[16], whereas PI is defined as any action initiated by a pharmacist resulting in a change of patient's management or therapy by the physician[17]. In France, the work group ''Standardisation et valorisation des activités de pharmacie clinique'' of the French Society of Clinical Pharmacy (SFPC) created and validated a tool for the standardization of the documentation of PIs performed in healthcare facilities and the CLEO© tool for assessing PIs' impacts[18,19]. A free access website observatory named Act-IP© was implemented in September 2006 allowing prospectively recording DRPs and PIs performed during daily practice, such as medication order review and multidisciplinary meetings[19,20].

The objective of this study was to assess the clinical impact of PIs in lung transplantation management. Specific aims were: i) to describe DRPs and PIs recorded on Act-IP© website during LT outpatients' management over a 7-year period, and ii) to evaluate their clinical impact.

## 2. Methods

### *2.1. Study design and population*

A retrospective observational study was performed on the PIs recorded on Act-IP© website observatory from 1st January 2009 to 31th December 2015 and related to the 152 LT recipients followed at the 2,200-bed Grenoble University Hospital over the 7-year period.



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All patients gave written informed consent to use their data for research. Study ethics approval was obtained on 28th March 2019 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

### *2.2. PCCP for LT outpatients*

Overall, clinical pharmacy services are provided by two senior and two resident pharmacists five days a week in our lung transplantation center. They include validating computerized medication orders from medication reconciliation and medical round attendance, implementing drug protocols, managing patient's education, improving medication use and optimizing therapeutic management according to patient's pathophysiological context for LT inpatients and outpatients.

The lung transplantation PCCP is a collaborative care program including physicians, nurses, dieticians, physiotherapists, and pharmacists. LT outpatients come in day hospital about every one to three months for monitoring according to medical appreciation. They are all individually interviewed for each medical visit by a clinical pharmacist or resident during 30-45 min in order to collect relevant data about drug handling, medication adherence, disease understanding, and to provide them counseling on medication and lifestyle. Clinical pharmacists interview 10 patients per week on average. In this collaborative model, the pharmacist can detect DRPs according to medication reconciliation as well as clinical and biological data, and provide recommendations (PIs) to nurses and physicians on therapeutic management. These recommendations are mostly performed before medical rounds and also transmitted through shared computer files; therapeutic optimizations are discussed weekly collaboratively during lung transplantation group meetings. There is oversight



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by the senior clinical pharmacist over the resident's recommendations every weeks before data recording.

### *2.3. Pharmacists' interventions data and Act-IP© database*

After registration on the Act-IP© website, pharmacists can record and analyze their interventions. Entering an intervention in the database took 15 minutes on average. The type of DRP and PI was classified according to the SFPC criteria using the report forms developed and validated for routine documentation[21]. The pharmacist prospectively completed the online report form specifying the date, pharmacist rank (senior or resident), patient demographic characteristics (age, sex), drug(s) involved in the DRP coded according to the Anatomical Therapeutic Chemical (ATC) classification[22], DRP description, PI description, and acceptance or not by the physician. Physician's acceptance was defined as prescription modification or change in medical care or therapeutic management.

### *2.4. Potential significance of PIs*

The impact of accepted PIs recorded on Act-IP© database was assessed according to a SFPC validated tool adapted for the French clinical practice named CLEO©. This tool includes a clinical dimension with seven categories (Nuisible, Null, Minor, Moderate, Major, Lethal, Non-determined), which evaluates patient's benefit according to the most likely case expected if no PI is performed[18,23] (an additional file shows this in more detail [see Appendices 1]).

An expert committee (a pharmacovigilance expert, a pulmonologist, and a clinical pharmacist) blindly evaluated each accepted PI by consensus from available data: age, gender, patient's history, a description of the DRP and the PI according to



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the classification of the SFPC, drug(s) involved, and clinical and biological information. In order to guarantee the quality of the interventions recording on Act-IP© database, data management was performed by a pharmacist resident before expert assessment.

### *2.5. Statistical analysis*

PI was the unit of analysis. Data were described as mean and standard deviation for quantitative variables, and frequency and percentage for qualitative variables. PI description included all data and the clinical impact was assessed for accepted PI because of change in patient management from pharmacist's evaluation. The clinical impact of PI was presented using bar charts, a matrix assessing the relationship between it and DRP, and a Pareto chart. The Pareto chart using "ABC analysis" is a useful tool for analysing what problems need attention first and is based on the "Pareto principle", a theory maintaining that 80% of the output in a given situation or system is produced by 20% of the input (group A). The other inputs are categorized in group B (15% of the output) and group C (the last 5% of the output)[24,25].

Data management and analysis were performed using EXCEL© software and SAS© 9.4 statistical software, SAS Institute, Cary, NC, USA.

## 3. Results

### *3.1. Characteristics of LT recipients*

A description of the LT recipients' cohort is presented in **Table 1.** PIs concerned male patients in 59.2% of cases and the mean age was 52 years old (range: 15-76 years old).



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### *3.2. Characteristics of DRPs and PIs*

During the 7-year study period, 1,569 PIs were recorded by 23 clinical pharmacists (seniors and residents) on the Act-IP© website observatory. These interventions were relied on 1,751 drugs, as PIs involved two or three drugs in 176 cases (11.2%) (*e.g.*, "drug-drug interaction" or "drug duplication"). Overall, 92.4% (n=1,449) of PIs were accepted by physicians (**Figure 1**).

Therapeutic classes mostly involved in DRPs were "antineoplastic and immunomodulating agents" (37.6%), "anti-infectives for systemic use" (22.6%), and "cardiovascular drugs" (9.2%) (**Table 2**).

The types of the DRPs and PIs are summarized in **Table 3**.

Overall, the most common types of DRPs identified by pharmacists were respectively "subtherapeutic dosage" (20.5%), "untreated indication" (19.6%), and "supratherapeutic dosage" (19.1%). Subtherapeutic dosage mainly concerned immunosuppressants (n=226, 70.2%), lipid modifying agents (n=18, 5.6%), and antivirals for systemic use (n=14, 4.3%). Untreated indication mostly concerned lipid modifying agents (n=38, 12.3%) and antianemic preparations (n=37, 12.0%). Supratherapeutic dosage mainly concerned immunosuppressants (n=205, 68.6%) and corticosteroids for systemic use (n=32, 10.7%).

Drug-drug interactions represented 8.4% (n=132) of DRPs. They mainly involved antimycotics for systemic use (n=99, 75.0%) and immunosuppressants (n=94, 71.2%). Among these drug-drug interactions, antimycotics for systemic use interacted with immunosuppressants in 76 cases (57.6%). Antimycotics for systemic use were mainly posaconazole (67.7%) and voriconazole (26.3%). Tacrolimus was the most implicated immunosuppressant in drug-drug interactions (87.2%). Only 11.4%



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(n=15) of the drug-drug interactions did not include neither immunosuppressant nor antimycotic for systemic use.

The PIs were mostly related to “dose adjustment” (43.8%), “addition of a new drug” (22.4%) and “drug discontinuation” (13.4%).

### *3.3. Potential clinical impact of PIs*

Clinical impact was assessed among the 1,448 accepted PIs (one PI could not be assessed because of lack of information) (**Figure 1**).

PIs had major (n=101, 7.0%), moderate (n=838, 57.9%) and minor (n=492, 34.0%) clinical impact (**Figure 2**). Two PIs could prevent an accident that could cause a potentially fatal complication. One was related to a pregnant woman with cystic fibrosis treated with teratogenic vitamin A. The other was related to a patient with an untreated persistent severe hypokalemia.

PIs with major clinical impact were mostly related to drug-drug interactions (n=40, 39.6%), involving immunosuppressants and antimycotics for systemic use (n=36). Those with moderate clinical impact were mainly due to subtherapeutic dosage (n=242, 28.9%), untreated indication (n=173, 20.6%) or supratherapeutic dosage (n=170, 20.3%) and mostly leading to dose adjustment (52.9%). PIs with minor clinical impact were mainly related to supratherapeutic dosage (n=99, 20.1%) and drug without indication (n=97, 19.7%).

Subtherapeutic dosage problem with moderate clinical impact was the most common type of accepted PIs (n=242) (**Figure 3**), involving tacrolimus in 40.9% of cases (n=99) followed by everolimus in 35.5% of cases (n=86). Among PIs with moderate clinical impact, supratherapeutic dosage (n=170) mainly involved tacrolimus (n=134, 78.8%) and untreated indication (n=173) concerned lipid modifying agents



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(n=31, 17.9%), antianemic preparations (n=28, 16.2%), and vaccines (n=27, 15.6%). 82.3% of drug-drug interactions were related to a moderate or major clinical impact (n=107) (**Figure 3**). Only 1.0% (n=15) of PIs had no clinical impact and was mainly related to drug without indication (**Figure 2**).

According to the Pareto chart, concerning PIs with major or lethal clinical impact (n=103) related to 144 drugs, immunosuppressants, antimycotics for systemic use, and antithrombotic agents had the greatest clinical impact (group A; **Figure 4**).

## 4. Discussion

Our study highlights a frequent intervention of clinical pharmacists in LT outpatient management with 1,569 PIs over seven years, representing about one intervention per day, as PIs have also an educational role decreasing DRPs rate over time. PIs were accepted by physicians almost all the time and mostly led to positive clinical impact for the patient.

In our study, the major causes of detected DRPs were an incorrect dose (39.6%), including both subtherapeutic and supratherapeutic dosages, and untreated indication (19.6%). These findings are in accordance to the literature in other solid organ transplantation[7,26–28]. Dosage problems are frequently detected because of the systematic pharmacist analysis of immunosuppressants and antimycotics blood trough concentrations before patient medication review and recommendations to physician, according to the routine therapeutic drug monitoring in our center. Untreated indication was related to drug stopped for contra-indication and not restarted (*e.g.*, everolimus after surgery), lack of premedication, necessary drugs to correct drug side effects, or non-prescribed drugs detected by medication reconciliation process. In Harrison *et al.*



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study related to lung transplantation[29], "adverse drug effect" was the most common type of DRP. However, they defined "adverse drug effect" as a "patient who is experiencing or at risk of an adverse drug reaction", which can include "supratherapeutic dosage" problem without any current adverse drug reaction. Immunosuppressants interacted with antifungal drugs in 57.6% of cases in our study. Of them, posaconazole and voriconazole are strong enzymatic inhibitors of cytochrome P450 3A4 which induce an increase of tacrolimus and everolimus elimination half-lives leading to potential toxicity. Multidisciplinary team should be also aware when antimycotics therapy is stopped, because of immunosuppressant trough concentration drop, and so potential graft rejection.

More than half of the PIs involved immunosuppressants (including glucocorticoids) and anti-infective drugs (63.4%). Immunosuppressants were the most concerned by PIs due to complex dosing regimens, high risk of drug-drug interactions, and adverse drug events[1–3]. High intervention rate related to anti-infective drugs may be because of the high frequency of use of these drugs in LT outpatients since they are prone to fungal, viral and bacterial infections despite prevention measures[30]. More specific analysis showed that tacrolimus and posaconazole were involved in about 30% of all drugs. Thus, clinical pharmacists should particularly monitor prescriptions of these two drugs. Cardiovascular system drugs were also frequently involved in PIs (9.2%) because of post-transplant hypertension or hyperlipidemia. Our results are in line with other previous studies in solid organ transplantation as immunosuppressants, cardiovascular drugs, and antimicrobials were involved in most cases[7,26,28,31].

The high acceptance rate found in our study confirms the relevance of PIs. This finding is in line with previous studies in clinical pharmacy[32] and more specifically in solid organ transplantation[7,26–29,31]. Our rate was similar to Ah *et al.* study (92.3%)



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related to more than 1,500 PIs in liver transplantation[7]. It can be explained by the "pro-active approach" of PIs in our lung transplantation center: clinical pharmacists interview outpatients before medical round and directly provide therapeutic suggestions to physicians during prescribing. Non-accepted PIs were mostly related to "untreated indication" (n=42) and "subtherapeutic dosage" (n=38) but the reason of non-acceptance was not explained in Act-IP© database. However, we can hypothesize that the reasons of non-acceptance may be related to stable patient condition without any adverse event or pharmacist's lack of information at the time of analysis.

Our study highlights the added value of clinical pharmacist in lung transplantation as clinical impact of accepted PIs was positive in 98.9% of cases and none had negative clinical impact. PIs allowed stopping major or lethal clinical outcomes in 7.1% of cases. DRPs to be detected as a priority were wrong dosage and untreated indication problems, associated with a moderate clinical impact in almost 70% of cases. The clinical impact was more important for subtherapeutic dosage problem than for supratherapeutic dosage problem, according to the risk of graft rejection. Clinical pharmacists should be aware of drug-drug interactions as they were related to moderate or major clinical impact in more than 80% of cases. The Pareto chart revealed that immunosuppressants, antimycotics for systemic use, and antithrombotic agents were the most implied drug classes in PIs with major or lethal clinical impact which require pharmacists' attention: clinical pharmacists took proactive steps with the transplant team to resolve these problems and developed or optimized protocols such as azole initiation monitoring recommendations.

One of the major strengths of this retrospective study relied on assessing clinical pharmacist's recommendations over a long period in a lung transplantation center with



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a full time pharmacist involvement, contrary to previous studies[7,26,27,29,31]. A double quality control process was performed to guarantee data reliability. PIs' impact was assessed by consensus of a multidisciplinary expert committee, including a pulmonologist. Only accepted PIs were evaluated because they represented the real impact of the pharmacist in LT outpatients' management. We used a new validated tool to assess the clinical impact of PIs[18]. The CLEO© tool has been recently created according to different scales available in the literature[23] and provided suitable inter-rater and intra-rater reliabilities. We acknowledge that the use of a new tool adapted to clinical practice for assessing clinical impact of PIs does not allow any comparison with previous studies in several solid organ transplantation[7,26,27,29,31], which mainly used Overhage *et al.* and Hatoum *et al.* scales[33,34]. However, we provided a new insight to assess the clinical impact of PIs by using the Pareto chart, a quality control tool which highlights drug groups that should be targeted in priority when pharmacists' time is lacking.

Some limitations have to be underlined. All the DRPs may be not detected by clinical pharmacists, because of pharmacist residents' lack of experience or pharmacist's lack of time. Indeed, each pharmacist resident is trained by a senior pharmacist at the beginning of his internship but without reaching senior's experience level, that is why the pharmacist controlled all recommendations to make sur they were optimized. In addition, not all identified DRPs may be recorded on the Act-IP© database, which may lead to an underestimate of DRPs prevalence. We acknowledge that there was no control group in this study. However, with a high acceptance rate and high significance of PIs, conducting randomized controlled trial may provoke ethical issues.



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Lung transplant recipients require more and more organized multidisciplinary care to improve effective and safe drug use. In our collaborative model, clinical pharmacist plays an important role as an expert in drug therapy to detect and resolve DRPs for each outpatient's clinic visit and provides relevant PIs to physicians. This study demonstrates the added value of clinical pharmacists in collaborative practice model in lung transplantation care and also provides information to target PIs in the future.

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**Patient and public involvement:**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Ethics approval and consent to participate:**

All patients gave written informed consent to use their data for research. Study ethics approval was obtained on 28 March 2019 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

**Conflict of interest:**

The authors declare that they have no competing interests.

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**Authors' contributions:**

MD, SC and PB designed the study and wrote the manuscript. MD, PB, SC, ML and BC performed data analysis.

All authors provided comments, participated in the critical revision of the manuscript, and approved the final version.



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**Checklist:**

See Appendices 2: *Check-list PaCIR.*

**Data sharing statement:**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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## REFERENCES


1. Monchaud C, Marquet P. Pharmacokinetic optimization of immunosuppressive therapy in thoracic transplantation: part I. *Clin Pharmacokinet*. 2009;48(7):419-462.

2. Monchaud C, Marquet P. Pharmacokinetic optimization of immunosuppressive therapy in thoracic transplantation: part II. *Clin Pharmacokinet*. 2009;48(8):489-516.

3. Sikma MA, van Maarseveen EM, van de Graaf EA, et al. Pharmacokinetics and Toxicity of Tacrolimus Early After Heart and Lung Transplantation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2015;15(9):2301-2313.

4. Bedouch P, Roustit M, Quetant S, et al. Development of a pharmacist collaborative care program for pulmonary arterial hypertension. *Int J Clin Pharm*. 2011;33(6):898-901.

5. Mitchell JF. Pharmacist involvement as a member of a renal transplant team. *Am J Hosp Pharm*. 1976;33(1):55-58.

6. Burckart GJ. Transplant pharmacy: 30 years of improving patient care. *Ann Pharmacother*. 2007;41(7):1261-1263.

7. Ah Y-M, Lee J-Y, Moon M-R, et al. Clinical and economic evaluation of pharmacists' contribution to patient care on a multi-disciplinary liver transplant team. *Int J Clin Pharmacol Ther*. 2016;54(2):102-109.




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8. Musgrave CR, Pilch NA, Taber DJ, et al. Improving transplant patient safety through pharmacist discharge medication reconciliation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2013;13(3):796-801.

9. Asavakarn S, Sirivatanauksorn Y, Promraj R, et al. Systematic Pharmaceutical Educational Approach to Enhance Drug Adherence in Liver Transplant Recipients. *Transplant Proc*. 2016;48(4):1202-1207.

10. Monnier G, Charpiat B, Serratrice F, Bossaert S, Fourcade N, Ducerf C. [Evaluation of drug therapy knowledge in liver transplant patients after pharmacy counseling]. *Therapie*. 2003;58(4):305-311.

11. Maldonado AQ, Weeks DL, Bitterman AN, et al. Changing transplant recipient education and inpatient transplant pharmacy practices: a single-center perspective. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm*. 2013;70(10):900-904.

12. Joost R, Dörje F, Schwitulla J, Eckardt K-U, Hugo C. Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2014;29(8):1597-1607.

13. Trofe-Clark J, Kaiser T, Pilch N, Taber D. Value of solid organ transplant-trained pharmacists in transplant infectious diseases. *Curr Infect Dis Rep*. 2015;17(4):475.



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14. Schuh MJ, Massoglia G. Pharmacist Impact on Tacrolimus Serum Concentrations in Liver Transplant Patients. *Consult Pharm J Am Soc Consult Pharm*. 2018;33(5):268-272.

15. Alloway RR, Dupuis R, Gabardi S, et al. Evolution of the role of the transplant pharmacist on the multidisciplinary transplant team. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2011;11(8):1576-1583.

16. *Classification for Drug Related Problems. The PCNE Classification*. Pharmaceutical Care Network Europe Foundation; 2017.

17. Dooley MJ, Allen KM, Doecke CJ, et al. A prospective multicentre study of pharmacist initiated changes to drug therapy and patient management in acute care government funded hospitals. *Br J Clin Pharmacol*. 2004;57(4):513-521.

18. Vo TH. *Evaluation of the Potential Impact of Pharmacist Interventions : Development and Validation of the CLEO Multidimensional Tool*. Grenoble, France: University Grenoble Alpes; 2015.

19. Allenet B, Bedouch P, Rose F-X, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. *Pharm World Sci PWS*. 2006;28(4):181-188.

20. Bedouch P, Charpiat B, Roubille R, et al. [Website of the French Society of Clinical Pharmacy for the analysis of pharmaceutical interventions: purpose, instructions and perspectives]. *J Pharm Clin*. 2007;26(1):40-44.

21. Conort O, Bedouch P, Juste M. [Validation of an instrument for the codification of clinical pharmacy interventions]. *J Pharm Clin*. 2004;23:141-147.



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22. *Guidelines for ATC Classification and DDD Assignment 2018*. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology; 2017.

23. Vo T-H, Charpiat B, Catoire C, et al. Tools for Assessing Potential Significance of Pharmacist Interventions: A Systematic Review. *Drug Saf*. 2016;39(2):131-146.

24. Pareto V. *Traité de Sociologie Générale*. 1re édition. Librairie Droz; 1917.

25. Blokdyk G. *ABC Analysis: Complete Self-Assessment Guide*. CreateSpace Independent Publishing Platform, 2018

26. Chisholm MA, Vollenweider LJ, Mulloy LL, Jagadeesan M, Wade WE, DiPiro JT. Direct patient care services provided by a pharmacist on a multidisciplinary renal transplant team. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm*. 2000;57(21):1994-1996.

27. Lima LF, Martins BCC, Oliveira FRP de, et al. Pharmaceutical orientation at hospital discharge of transplant patients: strategy for patient safety. *Einstein Sao Paulo Braz*. 2016;14(3):359-365.

28. Stemer G, Lemmens-Gruber R. Clinical pharmacy services and solid organ transplantation: a literature review. *Pharm World Sci PWS*. 2010;32(1):7-18.

29. Harrison JJ, Wang J, Cervenko J, et al. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. *Clin Transplant*. 2012;26(2):E149-157.

30. Nosotti M, Tarsia P, Morlacchi LC. Infections after lung transplantation. *J Thorac Dis*. 2018;10(6):3849-3868.



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31. Wang HY, Chan ALF, Chen MT, Liao CH, Tian YF. Effects of pharmaceutical care intervention by clinical pharmacists in renal transplant clinics. *Transplant Proc*. 2008;40(7):2319-2323.

32. Viktil KK, Blix HS. The impact of clinical pharmacists on drug-related problems and clinical outcomes. *Basic Clin Pharmacol Toxicol*. 2008;102(3):275-280.

33. Hatoum HT, Hutchinson RA, Witte KW, Newby GP. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. *Drug Intell Clin Pharm*. 1988;22(3):252-259.

34. Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacists' clinical activities. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm*. 1999;56(23):2444-2450.

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*Table 1: Baseline patients' characteristics (n=152)*

| Characteristic | n | (%) |
|---|---|---|
| **Age** [a] | | |
| 9-39 years old | 46 | (30.3) |
| 40-59 years old | 56 | (36.8) |
| >60 years old | 50 | (32.9) |
| **Sex** | | |
| Male | 90 | (59.2) |
| Female | 62 | (40.8) |
| **Indication for lung transplantation** | | |
| Chronic obstructive pulmonary disease | 79 | (52.0) |
| Cystic fibrosis | 39 | (25.6) |
| Diffuse interstitial lung disease | 22 | (14.5) |
| Pulmonary hypertension | 9 | (5.9) |
| Other | 3 | (2.0) |
| **Transplant procedure** | | |
| Double lung | 94 | (61.9) |
| Single lung | 54 | (35.5) |
| Heart/lung | 4 | (2.6) |
| **Retransplantation** | 3 | (2.0) |
| **Death during the study period** | 39 | (25.7) |
| **Number of lung transplantations during the study period** | 103 | (67.8) |

[a] Age at the time of the first lung transplantation



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*Table 2: Drugs involved in DRPs (n=1,751 drugs)*

| Drug groups (ATC Classification System) | N | (%) | Most frequent drugs (N) |
|---|---|---|---|
| **L - Antineoplastic and immunomodulating agents** | **659** | **(37.6)** | |
| Immunosuppressants (L04) | 657 | (37.5) | Tacrolimus (409), everolimus (190), mycophenolic acid (36) |
| **J - Anti-infectives for systemic use** | **397** | **(22.6)** | |
| Antimycotics for systemic use (J02A) | 175 | (10.0) | Posaconazole (118), voriconazole (41), itraconazole (9) |
| Direct acting antivirals (J05A) | 87 | (5.0) | Valganciclovir (80) |
| Immunoglobulins (J06B) | 37 | (2.1) | Human immunoglobulins (37) |
| Vaccines (J07) | 33 | (1.9) | Pneumococcal vaccines (18) |
| Sulfonamides and trimethoprim (J01E) | 21 | (1.2) | Sulfamethoxazole (21) |
| Macrolides, lincosamides and streptogramins (J01F) | 17 | (1.0) | Azithromycin (5), pristinamycin (4), clarithromycin (4) |
| Other antibacterials (J01X) | 9 | (0.5) | Colistin (8) |
| Aminoglycoside antibacterials (J01G) | 5 | (0.3) | Tobramycin (4) |
| Beta-lactam antibacterials (J01C + J01D) | 5 | (0.3) | Amoxicillin (2) |
| Quinolone antibacterials (J01M) | 4 | (0.2) | Ofloxacin (2) |
| **C – Cardiovascular system** | **162** | **(9.2)** | |
| Lipid modifying agents (C10) | 90 | (5.1) | Pravastatin (72), fenofibrat (10) |
| Calcium channel blockers (C08) | 23 | (1.3) | Lercanidipine (10), almodipine (10) |
| Agents acting on the renin-angiotensin system (C09) | 20 | (1.1) | Ramipril (9), perindopril (5), irbesartan (4) |
| Diuretics (C03) | 11 | (0.6) | Furosemide (8) |
| Cardiac therapy (C01) | 8 | (0.5) | Ivabradine (5) |
| Beta blocking agents (C07) | 6 | (0.3) | Atenolol (3) |
| **A - Alimentary tract and metabolism** | **141** | **(8.1)** | |
| Calcium (A12A) | 36 | (2.1) | Calcium (36) |
| Drugs for peptic ulcer and GORD (A02B) | 33 | (1.9) | Esomeprazole (26) |
| Vitamins (A11) | 29 | (1.7) | Vitamin D (18), Vitamin A (8) |
| Potassium (A12B) | 17 | (1.0) | Potassium (17) |
| Drugs used in diabetes (A10) | 8 | (0.5) | Repaglinide (5) |
| **B - Blood and blood forming organs** | **120** | **(6.9)** | |
| Iron preparations (B03A) | 71 | (4.1) | Iron bivalent, oral preparations (62) |
| Antithrombotic agents (B01A) | 22 | (1.3) | Fluindione (7), warfarin (8) |
| **H - Systemic hormonal preparations** | **60** | **(3.4)** | |
| Glucocorticoids (H02AB) | 58 | (3.3) | Prednisone (43), prednisolone (15) |
| **N – Nervous system** | **59** | **(3.4)** | |
| Analgesics (N02) | 28 | (1.6) | Paracetamol plain and combinations (13), morphine (6) |
| Psycholeptics (N05) | 11 | (0.6) | Hydroxyzine (4) |
| Psychoanaleptics (N06) | 10 | (0.6) | Mianserine (3), clomipramine (2), paroxetine (2) |
| Antiepileptics (N03) | 10 | (0.6) | Pregabalin (10) |
| **M - Musculo-skeletal system** | **51** | **(2.9)** | |
| Bisphosphonates (M05BA) | 44 | (2.5) | Zoledronic acid (40) |
| **Z - No ATC code** | **35** | **(2.0)** | Magnesium (31) |
| **P - Antiparasitic products, insecticides and repellants** | **28** | **(1.6)** | Pyrimethamine (25) |
| **V - Various** | **22** | **(1.3)** | Calcium folinate (19) |
| **R - Respiratory system** | **12** | **(0.7)** | |
| Drugs for obstructive airway diseases (R03) | 8 | (0.5) | Salbutamol (3), budesonide/formoterol (3) |
| **G - Genito-urinary system and sex hormones** | **3** | **(0.2)** | |
| **D - Dermatologicals** | **2** | **(0.1)** | |

DRPs: drug related problems, relied on 1,751 drugs, as each pharmacist's intervention involved two or three drugs in 176 cases (11.2%)
ATC: Anatomical Therapeutic Chemical classification system of drugs



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*Table 3: Characteristics of the DRPs and PIs*

| | Total (n=1,569) | Accepted (n=1,449) |
|---|---|---|
| **Characteristics** | **n (%)** | **n (%)** |
| **Drug related problems** | | |
| Subtherapeutic dosage | 322 (20.5) | 284 (19.6) |
| Untreated indication | 308 (19.6) | 266 (18.4) |
| Supratherapeutic dosage | 299 (19.1) | 291 (20.1) |
| Adverse drug reaction | 155 (9.9) | 145 (10.0) |
| Drug without indication | 148 (9.4) | 132 (9.1) |
| Drug-drug interaction | 132 (8.4) | 130 (9.0) |
| Drug monitoring | 85 (5.4) | 83 (5.7) |
| Improper administration | 42 (2.7) | 42 (2.9) |
| Non conformity to guidelines/contra-indication | 41 (2.6) | 40 (2.7) |
| Failure to receive drug | 37 (2.4) | 36 (2.5) |
| **Interventions** | | |
| Dose adjustment | 687 (43.8) | 635 (43.8) |
| Addition of a new drug | 351 (22.4) | 309 (21.3) |
| Drug discontinuation | 210 (13.4) | 191 (13.2) |
| Drug monitoring | 180 (11.5) | 175 (12.1) |
| Drug switch | 102 (6.5) | 100 (6.9) |
| Administration mode optimization | 37 (2.3) | 37 (2.6) |
| Change of administration route | 2 (0.1) | 2 (0.1) |

DRPs: drug related problems

PIs: pharmacists' interventions



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## FIGURE TITLES AND LEGENDS

Figure 1: Flowchart of pharmacist's interventions (PIs) recorded on Act-IP© database related to lung transplant outpatients Followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015

Figure 2: Clinical impact of accepted pharmacist's interventions (n=1,448) recorded on Act-IP© related to lung transplant outpatients Followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015

Figure 3: Clinical impact of accepted pharmacist's interventions (n=1,448), according to drug related problems, recorded on Act-IP© Related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015

Figure 4: Pareto chart of major and lethal clinical impact of accepted pharmacist's interventions (PIs) According to ATC groups (n=103), related to 144 drugs (group A: 80% of PIs; group B: 15% of PIs; group C: 5% of PIs)



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*Figure 1: Flowchart of pharmacist's interventions (PIs) recorded on Act-IP© database related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015*

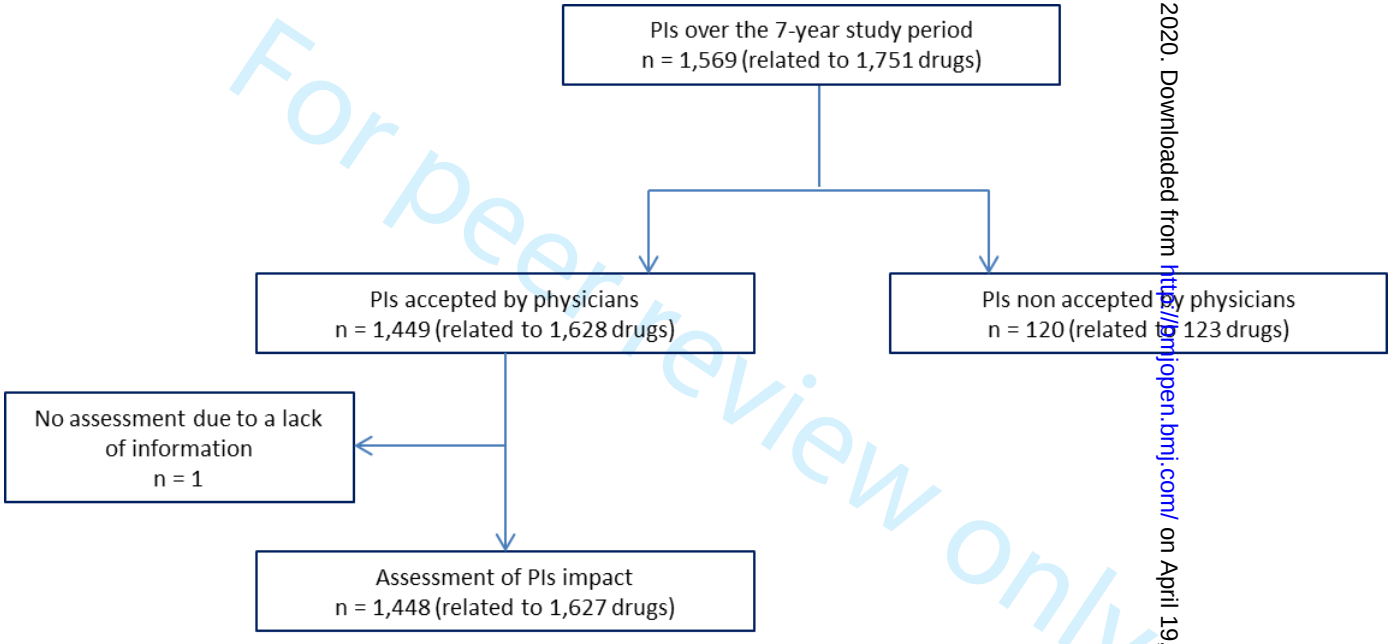


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*Figure 2: Clinical impact of accepted pharmacist's interventions (n=1,448) recorded on Act-IP© related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015*

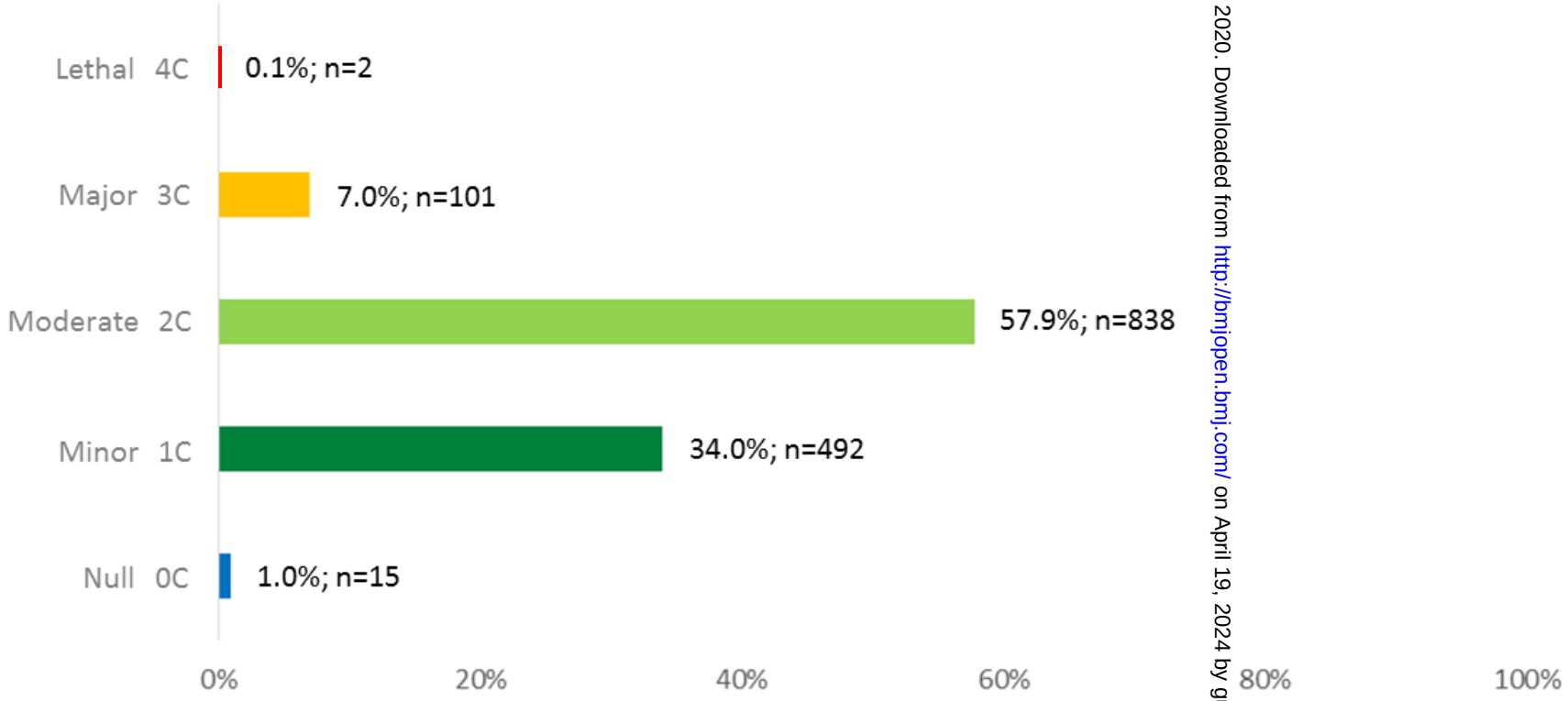


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*Figure 3: Clinical impact of accepted pharmacist's interventions (n=1,448), according to drug related problems, recorded on Act-IP© related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015*

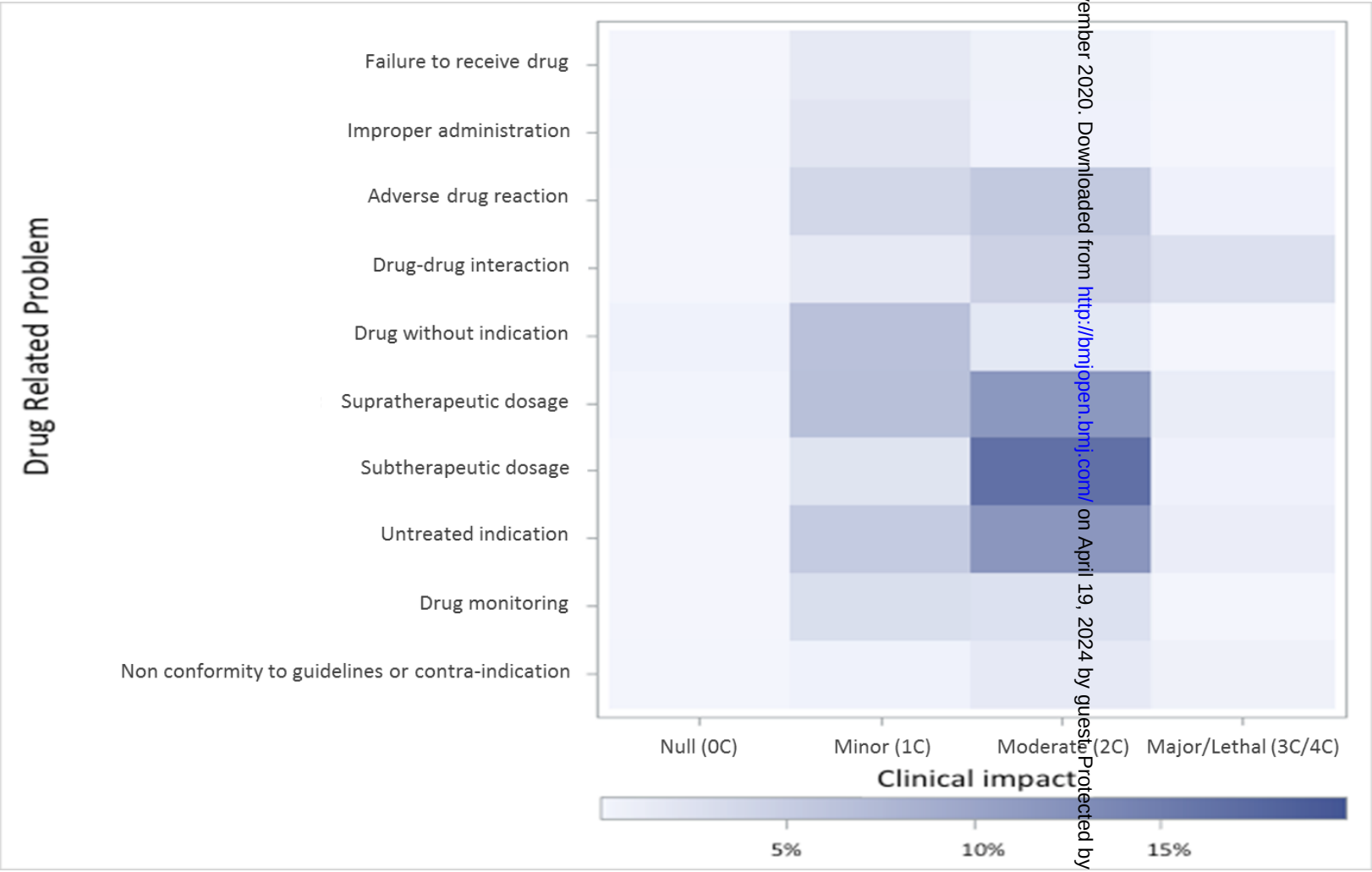


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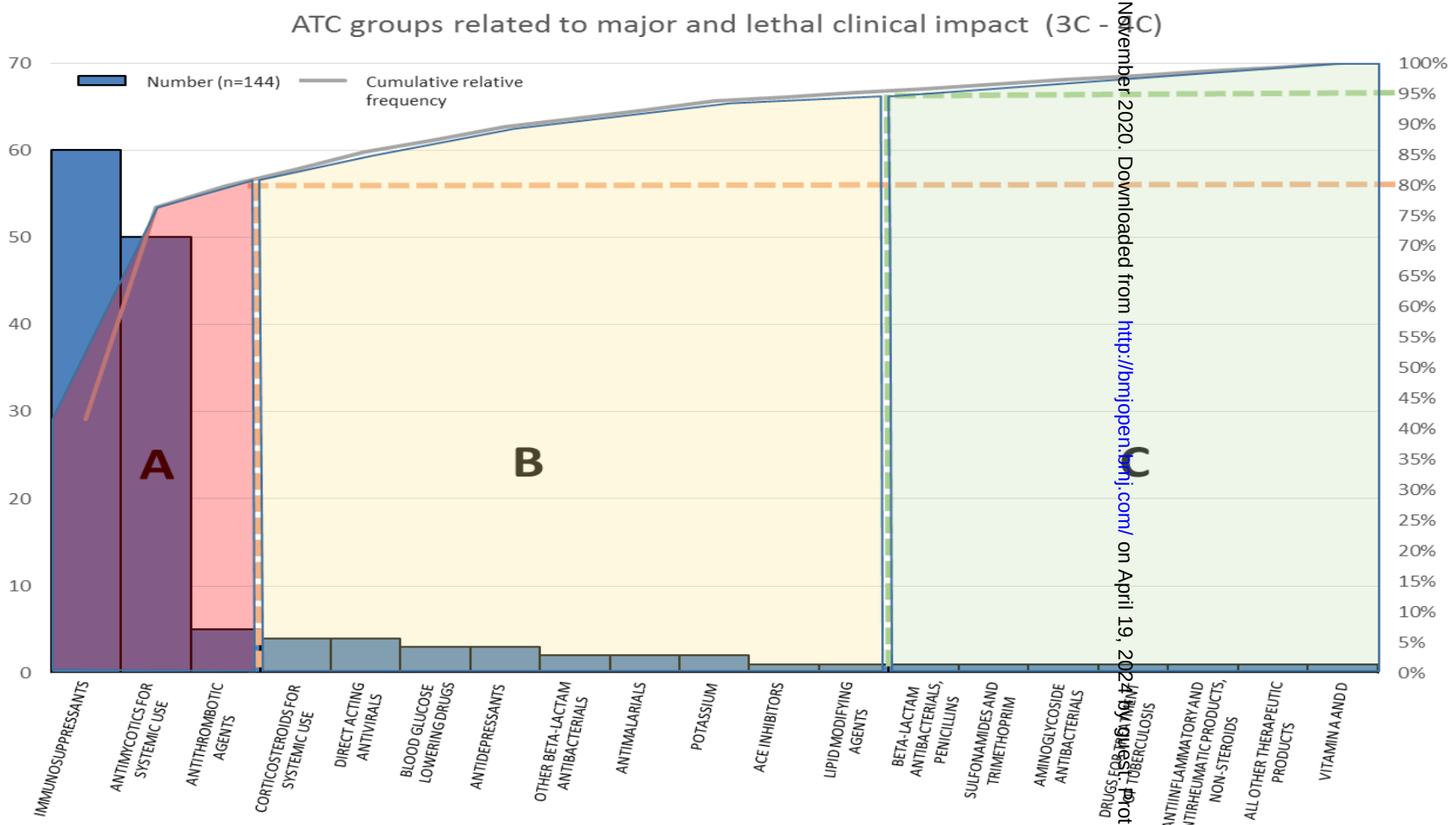
*Figure 4: Pareto chart of major and lethal clinical impact of accepted pharmacist's interventions (PIs) according to ATC groups (n=103), related to 144 drugs (group A: 80% of PIs; group B: 15% of PIs; group C: 5% of PIs)*

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**Supporting information: Check-list PaCIR**

## Pharmacist Patient Care Intervention Reporting checklist:PaCIR

PaCIR is designed to guide authors to include sufficient intervention details so as to improve the consistency in medical literature reporting of pharmacists' patient care interventions. Importantly, this checklist is designed to supplement (not replace) the primary literature reporting tool that most accurately reflects study design. Please include with submission the completed primary reporting guideline used. For help selecting primary checklist, please see http://www.equator-network.org/toolkits/selecting-the-appropriate-reporting-guideline/. Both completed checklists should be referenced in author's cover letter and included in submission packet.

**For each element of the intervention reported in PaCIR, please indicate if it is:**

- Applicable, Present (If yes to both, include in cell the section/page/line where reviewer may find it)
- Applicable, Absent (If an element is not present but applicable, indicate with a checkmark or "X". For each instance, author is strongly encouraged to include in the methods or limitations section of the manuscript or cover letter to editor why it is not present.)
- Not Applicable (Indicate with a checkmark or "X")

| **Primary Guideline used:** |
|---|
| **Intervention Preferred MeSH Terms:** |

| **CRITICAL ELEMENT:** **For each element below, denote if it is:** | **Applicable, Present*** | **Applicable, Absent**** | **Not Applicable** |
|---|---|---|---|
| 1. (**Replicability**) Sufficient description ofintervention to permit implementation under similar circumstances. | Section 2.2 (p9) | | |
| 2. (**Patient Population**) Sufficient descriptors of intervention recipients (and/or population) to assess generalizability. | Section 2.1 (p8)/Table 1 | | |
| 3. (**Patient / Other Data Sources**) Sufficient description of the source(s) and mechanism(s) by which patient or other data for the intervention were obtained or accessed. | Section 2.3 (p10) | | |
| 4. (**Environment**) Sufficient description of geographic and/or physical location(s) where intervention occurred, including any necessary infrastructure. | Sections 2.1 (p8) + 2.2 (p9) /Introduction (l160) | | |
| 5. (**Delivery**) Sufficient description of mode(s) of intervention delivery | Section 2.2 (p9) | | |
| 6. (**Frequency and Duration**) Sufficient description of frequency, number, and duration of session(s) for the intervention. | Section 2.2 (p9) | | |
| 7. (**Pharmacist Role / Responsibility**) Sufficient description of the roles/responsibilities of the pharmacist(s) and others involved in the intervention, including pharmacist-specific skills training. | Section 2.2 (p9) | | |
| 8. (**Attribution**) Sufficient description of the degree to which the outcomes are directly attributable to the roles/responsibilities of the pharmacist. | Discussion p17 (Limitations) | | |
| 9. (**Unique Attributes**) Sufficient description of factors not addressed in other elements that may impact replication. | Introduction p7 ; l160 | | |

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# TITLE PAGE

**Title:** Clinical evaluation of pharmacists' interventions on multidisciplinary lung transplant outpatients' management: results of a 7-year observational study

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## ABSTRACT

Objectives: Lung transplant (LT) recipients require multidisciplinary care because of the complexity of therapeutic management. Pharmacists are able to detect drug related problems and provide recommendations to physicians through pharmacists' interventions (PIs). We aimed at assessing the clinical impact of PIs on therapeutic management in LT outpatients.

Design: Data were collected prospectively from a LT recipients cohort during 7 years. A multidisciplinary committee assessed retrospectively the clinical impact of accepted PIs.

Setting: French University Hospital.

Participants: LT outpatients followed from 2009 to 2015.

Primary outcome measures: Clinical impact of PIs performed by pharmacists using the CLEO© tool and the Pareto chart.

Results: 1,449 PIs led to a change in patient therapeutic management and were mainly related to wrong dosage (39.6%) and untreated indication (19.6%). The clinical impact of PIs was "avoids fatality", "major" and "moderate", in 0.1%, 7.0%, and 57.9%, respectively. Immunosuppressants, antimycotics for systemic use, and antithrombotic agents had the greatest clinical impact according to the Pareto chart. PIs related to drug-drug interactions (10%) mainly had a moderate and major clinical impact (82.3%, $p < 0.0001$).

Conclusion: Clinical pharmacists play a key role for detecting DRPs mostly leading to a change in therapeutic management among LT outpatients. Our study provides a new insight to analyze the clinical impact of pharmacists' interventions in order to target PIs




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which have most value and contribute to patient care through interdisciplinary approach.

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**Article Summary: strengths and limitations of this study**

- Very few studies highlighted the clinical pharmacists' key role for optimizing therapeutic management in lung transplant outpatients
- A strength of this study is the assessment of pharmacist's clinical impact through a new validated scale and the analysis according to the Pareto principle
- Another strength is that pharmacist's added value is underlined through a collaborative practice model in lung transplantation over a 7-year period
- The main limitation was the retrospective assessment of clinical impact in a single center study
- Another limitation was not to be able to follow patients longitudinally through the anonymized database

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## MAIN TEXT

## 1. Introduction

Lung transplantation is an established treatment for patients with end-stage lung disease. Lung transplant (LT) recipients require multidisciplinary care because of the complexity of long-term immunosuppressive therapy and other specific therapies with narrow therapeutic index, leading to potential severe adverse drug events and drug-drug interactions[1–3]. Involving pharmacists in a multidisciplinary transplant care teams may improve medication use[4] and some studies have highlighted the positive impact of the clinical pharmacist's involvement in solid organ transplantation since 1976[5,6]. Transplant pharmacists may reduce medication errors, improve patient's education and his drug knowledge as well as detect drug related problems (DRPs)[7–10] ; they decrease the average hospital length of stay[11] and improve transplant recipients medication's adherence by providing intensified pharmaceutical care during the first post-transplant year[12]. Clinical pharmacist is also an essential member of the transplant team for the prevention and treatment of transplant infectious diseases[13], and for managing tacrolimus dosage[14]. However, pharmaceutical care in LT recipients is less studied than in renal or liver transplantation and the impact of clinical pharmacists' interventions (PIs) is poorly studied in lung transplantation as only one study in Canada with a small sample size was reported[15].

A Pharmacist Collaborative Care Program (PCCP) has been initiated in the lung transplantation center of Grenoble University Hospital (France) since 2008. There is no current accreditation for transplant pharmacist in our country but our lung transplantation center is approved by the *French Biomedicine Agency* and involves



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pharmacists as experts in drug therapy[16]. This program includes patient interviews and medication review during which pharmacists can detect DRPs and transmit PIs to physicians. DRP is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes[17], whereas PI is defined as any action initiated by a pharmacist resulting in a change of patient's management or therapy by the physician[18]. In France, the work group ''Standardisation et valorisation des activités de pharmacie clinique'' of the French Society of Clinical Pharmacy (SFPC) created and validated a tool for the standardization of the documentation of PIs performed in healthcare facilities and the CLEO© tool for assessing PIs' impacts[19,20]. A free access website observatory named Act-IP© was implemented in September 2006 allowing prospectively recording DRPs and PIs performed during daily practice, such as medication order review and multidisciplinary meetings[20,21].

The objective of this study was to assess the clinical impact of PIs in lung transplantation management. Specific aims were: i) to describe DRPs and PIs recorded on Act-IP© website during LT outpatients' management over a 7-year period, and ii) to evaluate their clinical impact.

## 2. Methods

### *2.1. Study design and population*

A retrospective observational study was performed on the PIs recorded on Act-IP© website observatory from 1st January 2009 to 31th December 2015 and related to the 152 LT recipients followed at the 2,200-bed Grenoble University Hospital over the 7-year period. Patients were eligible if they were lung transplanted before 1st



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January 2009 or between 1st January 2009 and 31th December 2015 according to our computerized hospital register of transplantation.

All patients gave written informed consent to use their data for research. Study ethics approval was obtained on 28th March 2019 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

**Patient and public involvement:**

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### *2.2. PCCP for LT outpatients*

Overall, clinical pharmacy services are provided since 2008 by two senior and two resident pharmacists five days a week in our lung transplantation center. They include validating computerized medication orders from medication reconciliation and medical round attendance, implementing drug protocols, managing patient's education, improving medication use and optimizing therapeutic management according to patient's pathophysiological context for LT inpatients and outpatients.

The lung transplantation PCCP is a collaborative care program including physicians, nurses, dieticians, physiotherapists, and pharmacists. LT outpatients come in the 15-bed Pneumology day hospital about every one to three months for monitoring according to medical appreciation. They are all individually interviewed for each medical visit by a clinical pharmacist or resident during 30-45 min in order to collect relevant data about drug handling, medication adherence, disease understanding, and to provide them counseling on medication and lifestyle. Clinical pharmacists interview 10 LT outpatients per week on average, representing about 17% of the total number



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of outpatients visiting the day hospital. In this collaborative model, the pharmacist can detect DRPs according to medication reconciliation as well as clinical and biological data, and provide recommendations (PIs) to nurses and physicians on therapeutic management. These recommendations are mostly performed before medical rounds and also transmitted through shared computer files; therapeutic optimizations are discussed weekly collaboratively during lung transplantation group meetings. There is oversight by the senior clinical pharmacist over the resident's recommendations every week before data recording.

### *2.3. Pharmacists' interventions data and Act-IP© database*

After registration on the Act-IP© website, pharmacists can record and analyze their interventions. Entering an intervention in the database took 15 minutes on average. The type of DRP and PI was classified according to the SFPC criteria using the report forms developed and validated for routine documentation[22]. The pharmacist prospectively completed the anonymized online report form specifying the date, pharmacist rank (senior or resident), patient demographic characteristics (age, sex), drug(s) involved in the DRP coded according to the Anatomical Therapeutic Chemical (ATC) classification[23], DRP description, PI description, and acceptance or not by the physician. Physician's acceptance was defined as prescription modification or change in medical care or therapeutic management. This tool was designed to record PIs through one-time actions and does not allow to follow patients longitudinally.

### *2.4. Potential significance of PIs*

The impact of accepted PIs recorded on Act-IP© database was assessed according to a SFPC validated tool adapted for the French clinical practice named



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CLEO©. This tool includes a clinical dimension with several numeric levels including negative, null and positive impacts (Minor, Moderate, Major, Avoids fatality), and an open level "undetermined", which evaluates patient's benefit according to the most likely case expected if no PI is performed[19,24] (an additional file shows this in more detail [see Appendix 1]).

Clinical assessment was performed by an independent expert committee (a pharmacovigilance expert, a pulmonologist, and a clinical pharmacist) from Grenoble University Hospital during a face-to-face meeting. After the presentation by the meeting moderator of each accepted intervention, each expert independently and blindly evaluated the clinical impact of each of these interventions prior to discussion to reach an expert consensus from available data: age, gender, patient's history, a description of the DRP and the PI according to the classification of the SFPC, drug(s) involved, and clinical and biological information. No inter-rater agreement was measured as each PI was rated after expert consensus. In order to guarantee the quality of the interventions recording on Act-IP© database, data management was performed by a pharmacist resident before expert assessment.

### *2.5. Statistical analysis*

PI was the unit of analysis. Data were described as mean and standard deviation for quantitative variables, and frequency and percentage for qualitative variables. PI description included all data and the clinical impact was assessed for accepted PI because of change in patient management from pharmacist's evaluation. The clinical impact of PI was presented using bar charts, a matrix assessing the relationship between it and DRP, and a Pareto chart. The Pareto chart using "ABC analysis" is a useful tool for analyzing what problems need attention first and is based



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on the "Pareto principle", a theory maintaining that 80% of the output in a given situation or system is produced by 20% of the input (group A). The other inputs are categorized in group B (15% of the output) and group C (the last 5% of the output)[25,26]. Fisher's exact test was used to compare the distribution of DRPs according to the clinical impact levels. Cochran-Armitage test for trend was used to test the association between different types of DRPs (drug-drug interaction, drug without indication and drug monitoring) and the clinical impact level as ordinal variable.

Data management and analysis were performed using EXCEL© software and SAS© 9.4 statistical software, SAS Institute, Cary, NC, USA.

## 3. Results

### *3.1. Characteristics of LT recipients*

A description of the LT recipients' cohort is presented in **Table 1.** PIs concerned male patients in 59.2% of cases and the mean age was 52 years old (range: 15-76 years old).

### *3.2. Characteristics of DRPs and PIs*

During the 7-year study period, 1,569 PIs were recorded by 23 clinical pharmacists (seniors and residents) on the Act-IP© website observatory. These interventions were relied on 1,751 drugs, as PIs involved two or three drugs in 176 cases (11.2%) (*e.g.*, "drug-drug interaction" or "drug duplication"). Overall, 92.4% (n=1,449) of PIs were accepted by physicians (**Figure 1**).



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Therapeutic classes mostly involved in DRPs were “antineoplastic and immunomodulating agents” (37.6%), “anti-infectives for systemic use” (22.6%), and “cardiovascular drugs” (9.2%) (**Table 2**).

The types of the DRPs and PIs are summarized in **Table 3**.

Overall, the most common types of DRPs identified by pharmacists were respectively “subtherapeutic dosage” (20.5%), “untreated indication” (19.6%), and “supratherapeutic dosage” (19.1%). Subtherapeutic dosage mainly concerned immunosuppressants (n=226, 70.2%), lipid modifying agents (n=18, 5.6%), and antivirals for systemic use (n=14, 4.3%). Untreated indication mostly concerned lipid modifying agents (n=38, 12.3%) and antianemic preparations (n=37, 12.0%). Supratherapeutic dosage mainly concerned immunosuppressants (n=205, 68.6%) and corticosteroids for systemic use (n=32, 10.7%).

Drug-drug interactions represented 8.4% (n=132) of DRPs. They mainly involved antimycotics for systemic use (n=99, 75.0%) and immunosuppressants (n=94, 71.2%). Among these drug-drug interactions, antimycotics for systemic use interacted with immunosuppressants in 76 cases (57.6%). Antimycotics for systemic use were mainly posaconazole (67.7%) and voriconazole (26.3%). Tacrolimus was the most implicated immunosuppressant in drug-drug interactions (87.2%). Only 11.4% (n=15) of the drug-drug interactions did not include neither immunosuppressant nor antimycotic for systemic use.

The PIs were mostly related to “dose adjustment” (43.8%), “addition of a new drug” (22.4%) and “drug discontinuation” (13.4%).



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### *3.3. Potential clinical impact of PIs*

Clinical impact was assessed among the 1,448 accepted PIs (one PI could not be assessed because of lack of information) (**Figure 1**).

PIs had major (n=101, 7.0%), moderate (n=838, 57.9%) and minor (n=492, 34.0%) clinical impact (**Figure 2**). Two PIs could prevent an accident that could cause a potentially fatal complication. One was related to a pregnant woman with cystic fibrosis treated with teratogenic vitamin A. The other was related to a patient with an untreated persistent severe hypokalemia.

PIs with major clinical impact were mostly related to drug-drug interactions (n=40, 39.6%, $p < 0.0001$), involving immunosuppressants and antimycotics for systemic use (n=36). Those with moderate clinical impact were mainly due to subtherapeutic dosage (n=242, 28.9%), untreated indication (n=173, 20.6%) or supratherapeutic dosage (n=170, 20.3%) and mostly leading to dose adjustment (52.9%). PIs with minor clinical impact were mainly related to supratherapeutic dosage (n=99, 20.1%) and drug without indication (n=97, 19.7%). There was a positive association between “drug-drug interactions” DRPs and the clinical impact level ($p < 0,0001$) whereas “drug without indication” and “drug monitoring” DRPs had a negative association with the clinical impact level ($p < 0,0001$).

Subtherapeutic dosage problem with moderate clinical impact was the most common type of accepted PIs (n=242) (**Figure 3**), involving tacrolimus in 40.9% of cases (n=99) followed by everolimus in 35.5% of cases (n=86). Among PIs with moderate clinical impact, supratherapeutic dosage (n=170) mainly involved tacrolimus (n=134, 78.8%) and untreated indication (n=173) concerned lipid modifying agents (n=31, 17.9%), antianemic preparations (n=28, 16.2%), and vaccines (n=27, 15.6%). 82.3% of drug-drug interactions were related to a moderate or major clinical impact



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(n=107) (**Figure 3**). Only 1.0% (n=15) of PIs had no clinical impact and was mainly related to drug without indication (**Figure 2**).

According to the Pareto chart, concerning PIs with major or "avoids fatality" clinical impact (n=103) related to 144 drugs, immunosuppressants, antimycotics for systemic use, and antithrombotic agents had the greatest clinical impact (group A; **Figure 4**).

## 4. Discussion

Our study highlights a frequent intervention of clinical pharmacists in LT outpatient management with 1,569 PIs over seven years, representing about one intervention per day, as PIs have also an educational role decreasing DRPs rate over time. PIs were accepted by physicians almost all the time and mostly led to positive clinical impact for the patient.

To the best of our knowledge, only one other study described pharmaceutical care intervention among LT outpatients[15]. This Canadian study was also a retrospective single center study but performed over a short period of seven months with senior clinical pharmacists providing patient care for only one-half day per week. Indeed, 55 DRPs were detected over 50 clinic visits concerning 43 patients mostly met only one time, during the early post-transplant period (< 3 months). This study mainly discussed patient satisfaction with pharmacist care rather than the type of DRPs and the clinical impact of PIs.

In our study, the major causes of detected DRPs were an incorrect dose (39.6%), including both subtherapeutic and supratherapeutic dosages, and untreated indication (19.6%). These findings are in accordance to the literature in other solid



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organ transplantation[7,27–29]. Dosage problems are frequently detected because of the systematic pharmacist analysis of immunosuppressants and antimycotics blood trough concentrations before patient medication review and recommendations to physician, according to the routine therapeutic drug monitoring in our center. Untreated indication was related to drug stopped for contra-indication and not restarted (*e.g.*, everolimus after surgery), lack of premedication, necessary drugs to correct drug side effects, or non-prescribed drugs detected by medication reconciliation process. In Harrison *et al.* study related to lung transplantation[15], "adverse drug effect" was the most common type of DRP. However, they defined "adverse drug effect" as a "patient who is experiencing or at risk of an adverse drug reaction", which can include "supratherapeutic dosage" problem without any current adverse drug reaction. Immunosuppressants interacted with antifungal drugs in 57.6% of cases in our study. Of them, posaconazole and voriconazole are strong enzymatic inhibitors of cytochrome P450 3A4 which induce an increase of tacrolimus and everolimus elimination half-lives leading to potential toxicity. Multidisciplinary team should be also aware when antimycotics therapy is stopped, because of immunosuppressant trough concentration drop, and so potential graft rejection.

More than half of the PIs involved immunosuppressants (including glucocorticoids) and anti-infective drugs (63.4%). Immunosuppressants were the most concerned by PIs due to complex dosing regimens, high risk of drug-drug interactions, and adverse drug events[1–3]. High intervention rate related to anti-infective drugs may be because of the high frequency of use of these drugs in LT outpatients since they are prone to fungal, viral and bacterial infections despite prevention measures[30]. More specific analysis showed that tacrolimus and posaconazole were involved in about 30% of all drugs. Thus, clinical pharmacists should particularly monitor prescriptions



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of these two drugs. Cardiovascular system drugs were also frequently involved in PIs (9.2%) because of post-transplant hypertension or hyperlipidemia. Our results are in line with other previous studies in solid organ transplantation as immunosuppressants, cardiovascular drugs, and antimicrobials were involved in most cases[7,27,29,31]. However, Harrison et al. reported that their interventions mainly involved gastrointestinal drugs without discussing this finding[15].

The high acceptance rate found in our study confirms the relevance of PIs. This finding is in line with previous studies in clinical pharmacy[32] and more specifically in solid organ transplantation[7,15,27–29,31]. Our rate was similar to Ah *et al.* study (92.3%) related to more than 1,500 PIs in liver transplantation[7]. It can be explained by the "pro-active approach" of PIs in our lung transplantation center: clinical pharmacists interview outpatients before medical round and directly provide therapeutic suggestions to physicians during prescribing. Non-accepted PIs were mostly related to "untreated indication" (n=42) and "subtherapeutic dosage" (n=38) but the reason of non-acceptance was not explained in Act-IP© database. However, we can hypothesize that the reasons of non-acceptance may be related to stable patient condition without any adverse event or pharmacist's lack of information at the time of analysis.

Our study highlights the added value of clinical pharmacist in lung transplantation as clinical impact of accepted PIs was positive in 98.9% of cases and none had negative clinical impact. PIs allowed stopping major or lethal clinical outcomes in 7.1% of cases. DRPs to be detected as a priority were wrong dosage and untreated indication problems, associated with a moderate clinical impact in almost 70% of cases. The clinical impact was more important for subtherapeutic dosage problem than for supratherapeutic dosage problem, according to the risk of graft rejection. Clinical pharmacists should be aware of drug-drug interactions as they were



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related to moderate or major clinical impact in more than 80% of cases. The Pareto chart revealed that immunosuppressants, antimycotics for systemic use, and antithrombotic agents were the most implied drug classes in PIs with major or lethal clinical impact which require pharmacists' attention: clinical pharmacists took proactive steps with the transplant team to resolve these problems and developed or optimized protocols such as azole initiation monitoring recommendations.

One of the major strengths of this retrospective study relied on assessing clinical pharmacist's recommendations over a long period in a lung transplantation center with a full time pharmacist involvement, contrary to previous studies[7,15,27,28,31]. A double quality control process was performed to guarantee data reliability. PIs' impact was assessed by consensus of a multidisciplinary expert committee, including a pulmonologist. Only accepted PIs were evaluated because they represented the real impact of the pharmacist in LT outpatients' management. We used a new validated tool to assess the clinical impact of PIs[19]. The CLEO© tool has been recently created according to different scales available in the literature[24] and provided suitable inter-rater and intra-rater reliabilities. This CLEO© tool was used to assess clinical impact of PIs on injectable antineoplastic prescriptions in a French Hospital Chemotherapy Preparation Unit[33] and was translated and validated in a German version[34]. We acknowledge that the use of a new tool adapted to clinical practice for assessing clinical impact of PIs does not allow any comparison with previous studies in several solid organ transplantation[7,15,27,28,31], which mainly used Overhage *et al.* and Hatoum *et al.* scales[35,36]. However, we provided a new insight to assess the clinical impact of PIs by using the Pareto chart, a quality control tool which highlights drug groups that should be targeted in priority when pharmacists' time is lacking.



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Some limitations have to be underlined. All the DRPs may be not detected by clinical pharmacists, because of pharmacist residents' lack of experience or pharmacist's lack of time. Indeed, each pharmacist resident is trained by a senior pharmacist at the beginning of his internship but without reaching senior's experience level, that is why the pharmacist controlled all recommendations to make sure they were optimized. In addition, not all identified DRPs may be recorded on the Act-IP© database although it was mandatory, which may lead to an underestimate of DRPs prevalence. This possible under-reporting could not be excluded, particularly for non-accepted PIs. Our data could not be presented in terms of patient proportion as all the PIs were recorded anonymously in the Act-IP© database. We acknowledge that there was no control group in this study. However, with a high acceptance rate and high significance of PIs, conducting randomized controlled trial may provoke ethical issues.

Lung transplant recipients require more and more organized multidisciplinary care to improve effective and safe drug use. In our collaborative model, clinical pharmacist plays an important role as an expert in drug therapy to detect and resolve DRPs for each outpatient's clinic visit and provides relevant PIs to physicians. This study demonstrates the added value of clinical pharmacists in collaborative practice model in lung transplantation care and also provides information to target PIs in the future.



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**Ethics approval and consent to participate:**

All patients gave written informed consent to use their data for research. Study ethics approval was obtained on 28 March 2019 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

**Conflict of interest:**

The authors declare that they have no competing interests.

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**Authors' contributions:**

All coauthors fulfill the criteria required for authorship. MD, SC and PB were responsible for study conception. MD performed data collection. MD and SC performed data analysis and interpretation, and drafted the manuscript. PB and JC revised the drafting for important intellectual content. ML, THV, HP, RM, BA, CP, AB, CSR and BC contributed with reviews of the final draft. All authors provided comments, and approved the final version to be published and are in agreement to be accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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**Checklist:**

See Research Check-list *STROBE*

**Data sharing statement:**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## REFERENCES


1. Monchaud C, Marquet P. Pharmacokinetic optimization of immunosuppressive therapy in thoracic transplantation: part I. *Clin Pharmacokinet*. 2009;48(7):419-462.

2. Monchaud C, Marquet P. Pharmacokinetic optimization of immunosuppressive therapy in thoracic transplantation: part II. *Clin Pharmacokinet*. 2009;48(8):489-516.

3. Sikma MA, van Maarseveen EM, van de Graaf EA, et al. Pharmacokinetics and Toxicity of Tacrolimus Early After Heart and Lung Transplantation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2015;15(9):2301-2313.

4. Bedouch P, Roustit M, Quetant S, et al. Development of a pharmacist collaborative care program for pulmonary arterial hypertension. *Int J Clin Pharm*. 2011;33(6):898-901.

5. Mitchell JF. Pharmacist involvement as a member of a renal transplant team. *Am J Hosp Pharm*. 1976;33(1):55-58.

6. Burckart GJ. Transplant pharmacy: 30 years of improving patient care. *Ann Pharmacother*. 2007;41(7):1261-1263.

7. Ah Y-M, Lee J-Y, Moon M-R, et al. Clinical and economic evaluation of pharmacists' contribution to patient care on a multi-disciplinary liver transplant team. *Int J Clin Pharmacol Ther*. 2016;54(2):102-109.

8. Musgrave CR, Pilch NA, Taber DJ, et al. Improving transplant patient safety through pharmacist discharge medication reconciliation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2013;13(3):796-801.

9. Asavakarn S, Sirivatanauksorn Y, Promraj R, et al. Systematic Pharmaceutical Educational Approach to Enhance Drug Adherence in Liver Transplant Recipients. *Transplant Proc*. 2016;48(4):1202-1207.

10. Monnier G, Charpiat B, Serratrice F, Bossaert S, Fourcade N, Ducerf C. [Evaluation of drug therapy knowledge in liver transplant patients after pharmacy counseling]. *Therapie*. 2003;58(4):305-311.

11. Maldonado AQ, Weeks DL, Bitterman AN, et al. Changing transplant recipient education and inpatient transplant pharmacy practices: a single-center perspective. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm*. 2013;70(10):900-904.

12. Joost R, Dörje F, Schwitulla J, Eckardt K-U, Hugo C. Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2014;29(8):1597-1607.

13. Trofe-Clark J, Kaiser T, Pilch N, Taber D. Value of solid organ transplant-trained pharmacists in transplant infectious diseases. *Curr Infect Dis Rep*. 2015;17(4):475.

14. Schuh MJ, Massoglia G. Pharmacist Impact on Tacrolimus Serum Concentrations in Liver Transplant Patients. *Consult Pharm J Am Soc Consult Pharm*. 2018;33(5):268-272.




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15. Harrison JJ, Wang J, Cervenko J, et al. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. *Clin Transplant*. 2012;26(2):E149-157.

16. Alloway RR, Dupuis R, Gabardi S, et al. Evolution of the role of the transplant pharmacist on the multidisciplinary transplant team. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2011;11(8):1576-1583.

17. *Classification for Drug Related Problems. The PCNE Classification*. Pharmaceutical Care Network Europe Foundation; 2017.

18. Dooley MJ, Allen KM, Doecke CJ, et al. A prospective multicentre study of pharmacist initiated changes to drug therapy and patient management in acute care government funded hospitals. *Br J Clin Pharmacol*. 2004;57(4):513-521.

19. Vo T-H. Evaluation of the potential impact of pharmacist interventions: development and validation of the CLEO multidimensional tool. Pharmaceutical sciences. Université Grenoble Alpes, 2015. English. ffNNT : 2015GREAS034ff. fftel-01315619

20. Allenet B, Bedouch P, Rose F-X, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. *Pharm World Sci PWS*. 2006;28(4):181-188.

21. Bedouch P, Charpiat B, Roubille R, et al. [Website of the French Society of Clinical Pharmacy for the analysis of pharmaceutical interventions: purpose, instructions and perspectives]. *J Pharm Clin*. 2007;26(1):40-44.

22. Conort O, Bedouch P, Juste M. [Validation of an instrument for the codification of clinical pharmacy interventions]. *J Pharm Clin*. 2004;23:141-147.

23. *Guidelines for ATC Classification and DDD Assignment 2018*. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology; 2017.

24. Vo T-H, Charpiat B, Catoire C, et al. Tools for Assessing Potential Significance of Pharmacist Interventions: A Systematic Review. *Drug Saf*. 2016;39(2):131-146.

25. Pareto V. *Traité de Sociologie Générale*. 1re édition. Librairie Droz; 1917.

26. Blokdyk G. *ABC Analysis: Complete Self-Assessment Guide*. CreateSpace Independent Publishing Platform, 2018

27. Chisholm MA, Vollenweider LJ, Mulloy LL, Jagadeesan M, Wade WE, DiPiro JT. Direct patient care services provided by a pharmacist on a multidisciplinary renal transplant team. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm*. 2000;57(21):1994-1996.

28. Lima LF, Martins BCC, Oliveira FRP de, et al. Pharmaceutical orientation at hospital discharge of transplant patients: strategy for patient safety. *Einstein Sao Paulo Braz*. 2016;14(3):359-365.

29. Stemer G, Lemmens-Gruber R. Clinical pharmacy services and solid organ transplantation: a literature review. *Pharm World Sci PWS*. 2010;32(1):7-18.

30. Nosotti M, Tarsia P, Morlacchi LC. Infections after lung transplantation. *J Thorac Dis*. 2018;10(6):3849-3868.



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31. Wang HY, Chan ALF, Chen MT, Liao CH, Tian YF. Effects of pharmaceutical care intervention by clinical pharmacists in renal transplant clinics. *Transplant Proc*. 2008;40(7):2319-2323.

32. Viktil KK, Blix HS. The impact of clinical pharmacists on drug-related problems and clinical outcomes. *Basic Clin Pharmacol Toxicol*. 2008;102(3):275-280.

33. Zecchini C, Vo T-H, Chanoine S, et al. Clinical, economic and organizational impact of pharmacist interventions on injectable antineoplastic prescriptions: a prospective observational study. *BMC Health Serv Res*. 2020;20(1).

34. Stämpfli D, Baumgartner P, Boeni F, Bedouch P, Lampert ML, Hersberger KE. Translation and validation of a tool to assess the impact of clinical pharmacists' interventions. *Int J Clin Pharm*. 2019;41(1):56-64.

35. Hatoum HT, Hutchinson RA, Witte KW, Newby GP. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. *Drug Intell Clin Pharm*. 1988;22(3):252-259.

36. Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacists' clinical activities. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm*. 1999;56(23):2444-2450.

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*Table 1: Baseline patients' characteristics (n=152)*

| Characteristic | n | (%) |
|---|---|---|
| **Age** [a] | | |
| 9-39 years old | 46 | (30.3) |
| 40-59 years old | 56 | (36.8) |
| >60 years old | 50 | (32.9) |
| **Sex** | | |
| Male | 90 | (59.2) |
| Female | 62 | (40.8) |
| **Indication for lung transplantation** | | |
| Chronic obstructive pulmonary disease | 79 | (52.0) |
| Cystic fibrosis | 39 | (25.6) |
| Diffuse interstitial lung disease | 22 | (14.5) |
| Pulmonary hypertension | 9 | (5.9) |
| Other | 3 | (2.0) |
| **Transplant procedure** | | |
| Double lung | 94 | (61.9) |
| Single lung | 54 | (35.5) |
| Heart/lung | 4 | (2.6) |
| **Retransplantation** | 3 | (2.0) |
| **Death during the study period** | 39 | (25.7) |
| **Number of lung transplantations during the study period** | 103 | (67.8) |

[a] Age at the time of the first lung transplantation



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*Table 2: Drugs involved in DRPs (n=1,751 drugs)*

| Drug groups (ATC Classification System) | N | (%) | Most frequent drugs (N) |
|---|---|---|---|
| **L - Antineoplastic and immunomodulating agents** | **659** | **(37.6)** | |
| Immunosuppressants (L04) | 657 | (37.5) | Tacrolimus (409), everolimus (190), mycophenolic acid (36) |
| **J - Anti-infectives for systemic use** | **397** | **(22.6)** | |
| Antimycotics for systemic use (J02A) | 175 | (10.0) | Posaconazole (118), voriconazole (41), itraconazole (9) |
| Direct acting antivirals (J05A) | 87 | (5.0) | Valganciclovir (80) |
| Immunoglobulins (J06B) | 37 | (2.1) | Human immunoglobulins (37) |
| Vaccines (J07) | 33 | (1.9) | Pneumococcal vaccines (18) |
| Sulfonamides and trimethoprim (J01E) | 21 | (1.2) | Sulfamethoxazole (21) |
| Macrolides, lincosamides and streptogramins (J01F) | 17 | (1.0) | Azithromycin (5), pristinamycin (4), clarithromycin (4) |
| Other antibacterials (J01X) | 9 | (0.5) | Colistin (8) |
| Aminoglycoside antibacterials (J01G) | 5 | (0.3) | Tobramycin (4) |
| Beta-lactam antibacterials (J01C + J01D) | 5 | (0.3) | Amoxicillin (2) |
| Quinolone antibacterials (J01M) | 4 | (0.2) | Ofloxacin (2) |
| **C – Cardiovascular system** | **162** | **(9.2)** | |
| Lipid modifying agents (C10) | 90 | (5.1) | Pravastatin (72), fenofibrat (10) |
| Calcium channel blockers (C08) | 23 | (1.3) | Lercanidipine (10), almodipine (10) |
| Agents acting on the renin-angiotensin system (C09) | 20 | (1.1) | Ramipril (9), perindopril (5), irbesartan (4) |
| Diuretics (C03) | 11 | (0.6) | Furosemide (8) |
| Cardiac therapy (C01) | 8 | (0.5) | Ivabradine (5) |
| Beta blocking agents (C07) | 6 | (0.3) | Atenolol (3) |
| **A - Alimentary tract and metabolism** | **141** | **(8.1)** | |
| Calcium (A12A) | 36 | (2.1) | Calcium (36) |
| Drugs for peptic ulcer and GORD (A02B) | 33 | (1.9) | Esomeprazole (26) |
| Vitamins (A11) | 29 | (1.7) | Vitamin D (18), Vitamin A (8) |
| Potassium (A12B) | 17 | (1.0) | Potassium (17) |
| Drugs used in diabetes (A10) | 8 | (0.5) | Repaglinide (5) |
| **B - Blood and blood forming organs** | **120** | **(6.9)** | |
| Iron preparations (B03A) | 71 | (4.1) | Iron bivalent, oral preparations (62) |
| Antithrombotic agents (B01A) | 22 | (1.3) | Fluindione (7), warfarin (8) |
| **H - Systemic hormonal preparations** | **60** | **(3.4)** | |
| Glucocorticoids (H02AB) | 58 | (3.3) | Prednisone (43), prednisolone (15) |
| **N – Nervous system** | **59** | **(3.4)** | |
| Analgesics (N02) | 28 | (1.6) | Paracetamol plain and combinations (13), morphine (6) |
| Psycholeptics (N05) | 11 | (0.6) | Hydroxyzine (4) |
| Psychoanaleptics (N06) | 10 | (0.6) | Mianserine (3), clomipramine (2), paroxetine (2) |
| Antiepileptics (N03) | 10 | (0.6) | Pregabalin (10) |
| **M - Musculo-skeletal system** | **51** | **(2.9)** | |
| Bisphosphonates (M05BA) | 44 | (2.5) | Zoledronic acid (40) |
| **Z - No ATC code** | **35** | **(2.0)** | Magnesium (31) |
| **P - Antiparasitic products, insecticides and repellants** | **28** | **(1.6)** | Pyrimethamine (25) |
| **V - Various** | **22** | **(1.3)** | Calcium folinate (19) |
| **R - Respiratory system** | **12** | **(0.7)** | |
| Drugs for obstructive airway diseases (R03) | 8 | (0.5) | Salbutamol (3), budesonide/formoterol (3) |
| **G - Genito-urinary system and sex hormones** | **3** | **(0.2)** | |
| **D - Dermatologicals** | **2** | **(0.1)** | |

DRPs: drug related problems, relied on 1,751 drugs, as each pharmacist's intervention involved two or three drugs in 176 cases (11.2%)
ATC: Anatomical Therapeutic Chemical classification system of drugs



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*Table 3: Characteristics of the DRPs and PIs*

| | Total (n=1,569) | Accepted (n=1,449) |
|---|---|---|
| **Characteristics** | **n (%)** | **n (%)** |
| **Drug related problems** | | |
| Subtherapeutic dosage | 322 (20.5) | 284 (19.6) |
| Untreated indication | 308 (19.6) | 266 (18.4) |
| Supratherapeutic dosage | 299 (19.1) | 291 (20.1) |
| Adverse drug reaction | 155 (9.9) | 145 (10.0) |
| Drug without indication | 148 (9.4) | 132 (9.1) |
| Drug-drug interaction | 132 (8.4) | 130 (9.0) |
| Drug monitoring | 85 (5.4) | 83 (5.7) |
| Improper administration | 42 (2.7) | 42 (2.9) |
| Non conformity to guidelines/contra-indication | 41 (2.6) | 40 (2.7) |
| Failure to receive drug | 37 (2.4) | 36 (2.5) |
| **Interventions** | | |
| Dose adjustment | 687 (43.8) | 635 (43.8) |
| Addition of a new drug | 351 (22.4) | 309 (21.3) |
| Drug discontinuation | 210 (13.4) | 191 (13.2) |
| Drug monitoring | 180 (11.5) | 175 (12.1) |
| Drug switch | 102 (6.5) | 100 (6.9) |
| Administration mode optimization | 37 (2.3) | 37 (2.6) |
| Change of administration route | 2 (0.1) | 2 (0.1) |

DRPs: drug related problems

PIs: pharmacists' interventions



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## FIGURE TITLES AND LEGENDS

Figure 1: Flowchart of pharmacists' interventions (PIs) recorded on Act-IP© database related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015

Figure 2: Clinical impact of accepted pharmacists' interventions (n=1,448) recorded on Act-IP© database related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015

Figure 3: Clinical impact of accepted pharmacists' interventions (n=1,448), according to drug related problems, recorded on Act-IP© database related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015

Figure 4: Pareto chart of "major" and "avoids fatality" clinical impact of accepted pharmacists' interventions (PIs) according to ATC groups (n=103), related to 144 drugs (group A: 80% of PIs; group B: 15% of PIs; group C: 5% of PIs)



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*Figure 1: Flowchart of pharmacists' interventions (PIs) recorded on Act-IP© database related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015*

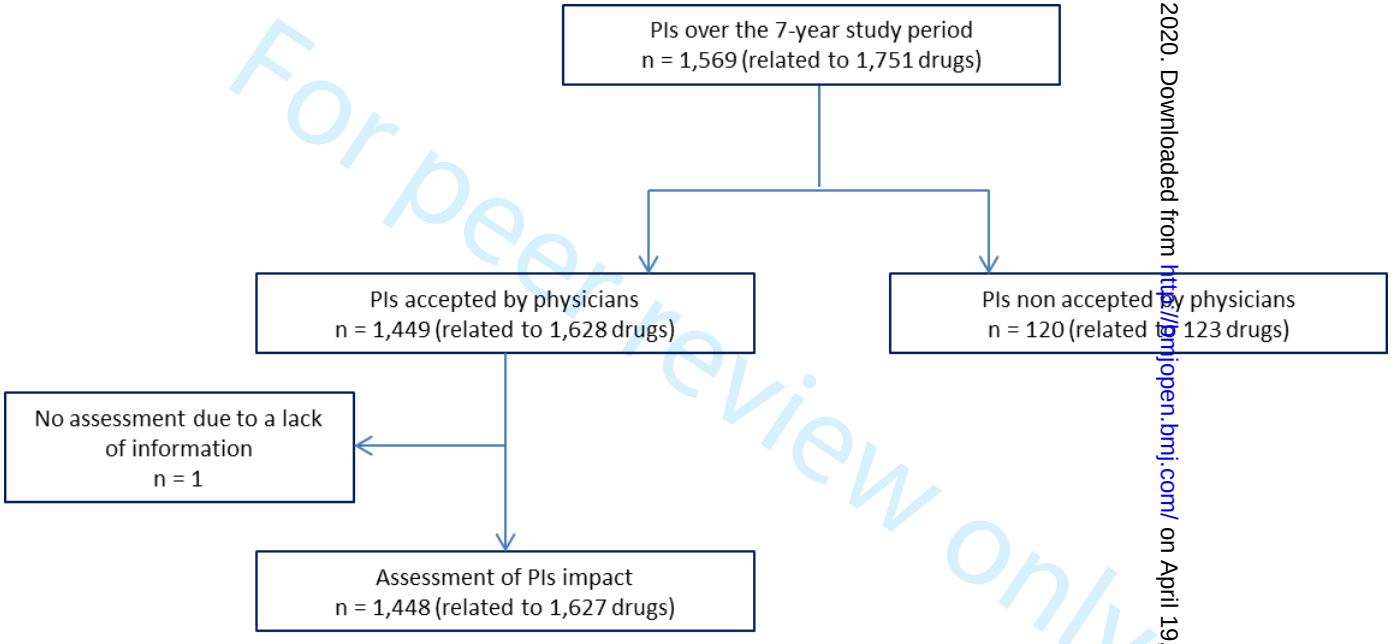


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*Figure 2: Clinical impact of accepted pharmacists' interventions (n=1,448) recorded on Act-IP© database related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015*

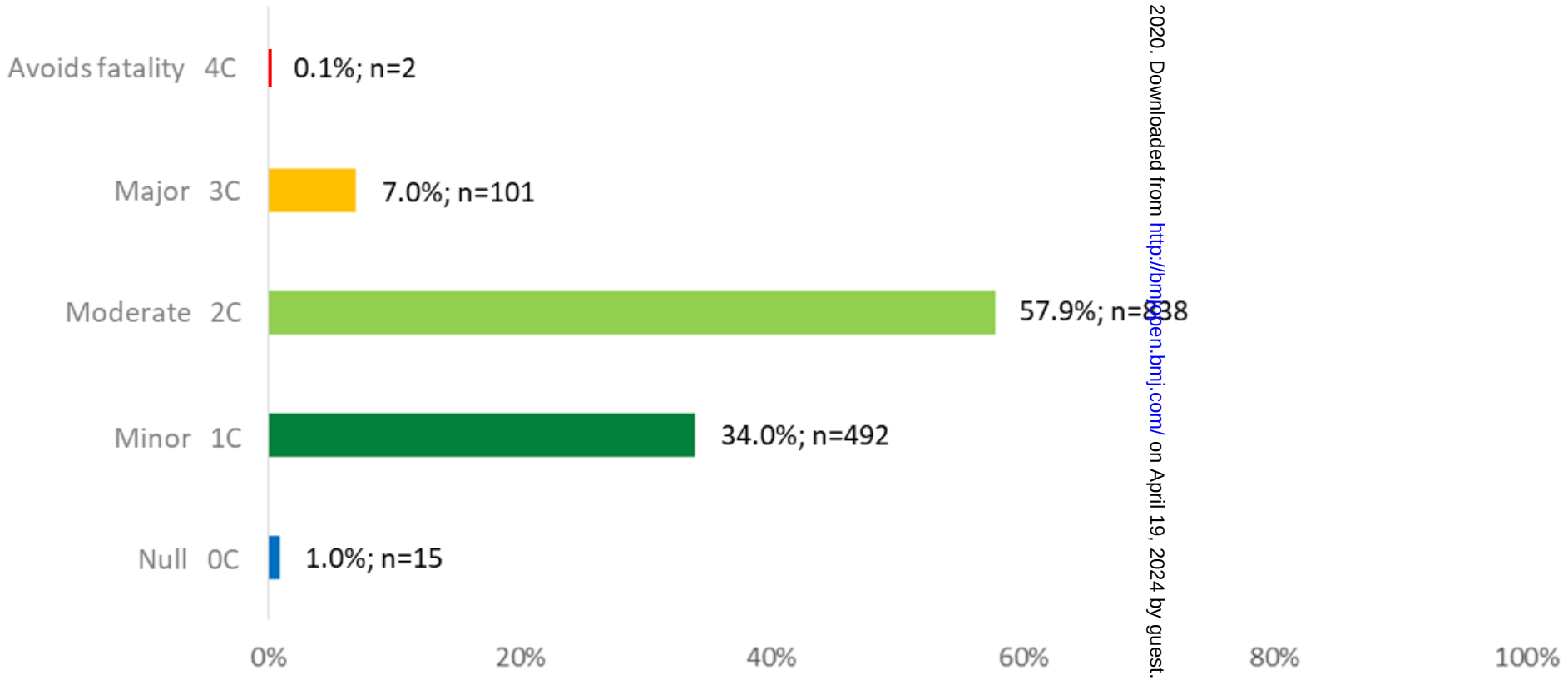


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*Figure 3: Clinical impact of accepted pharmacists' interventions (n=1,448), according to drug related problems, recorded on Act-IP© database related to lung transplant outpatients followed at Grenoble University Hospital from 1st January 2009 to 31th December 2015*

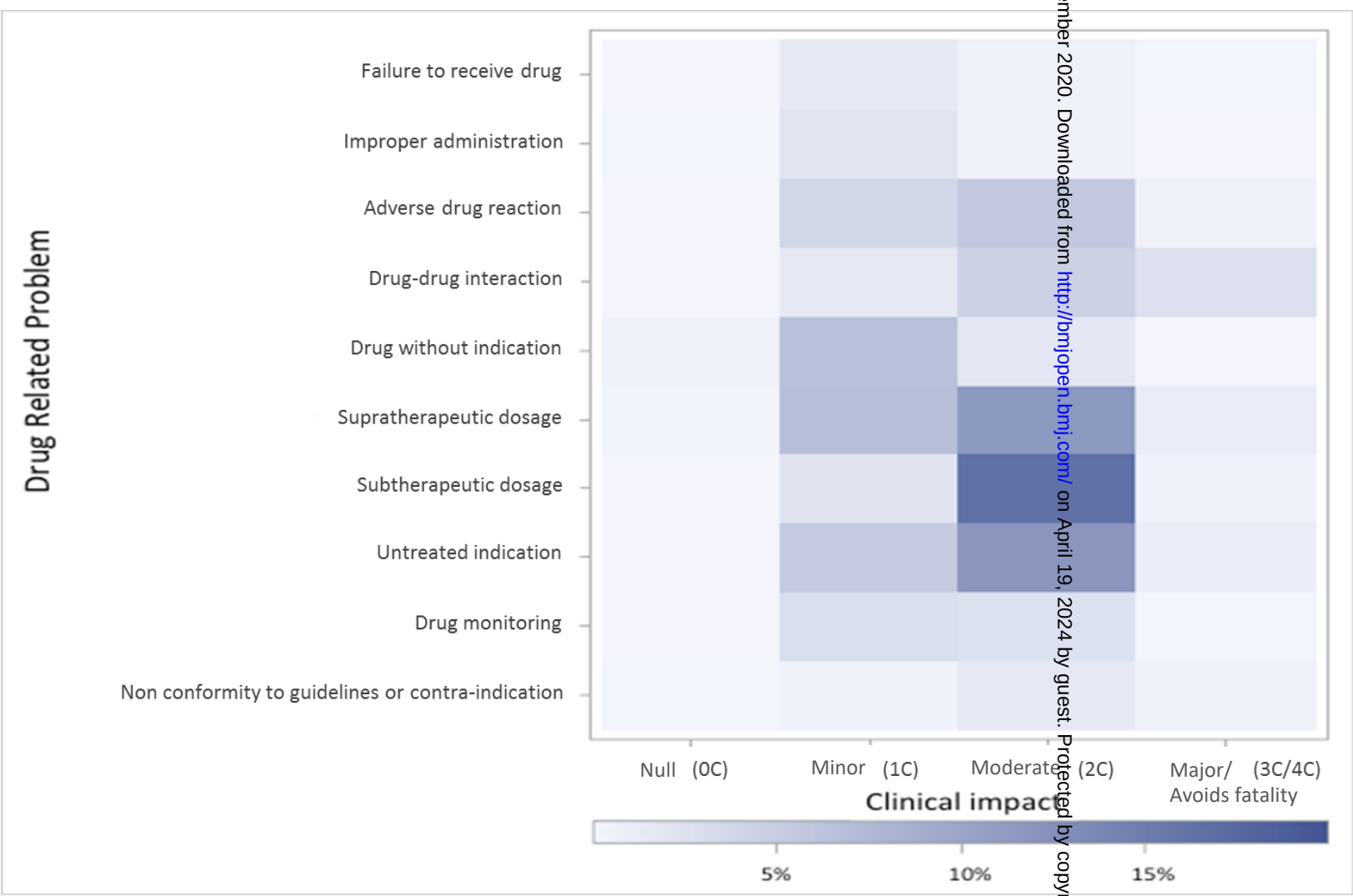




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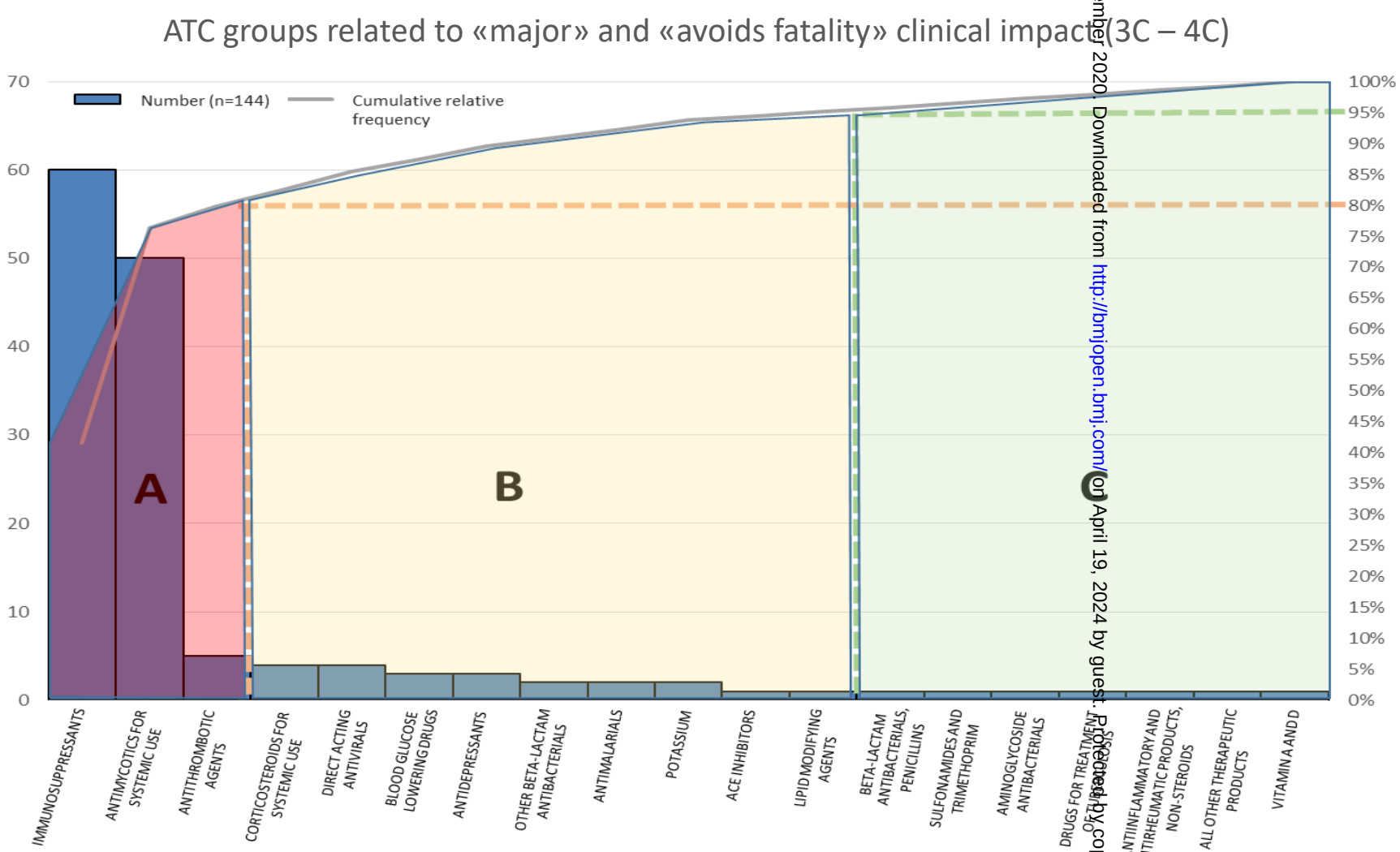
*Figure 4: Pareto chart of "major" and "avoids fatality" clinical impact of accepted pharmacists' interventions (PIs) according to ATC groups (n=103), related to 144 drugs (group A: 80% of PIs; group B: 15% of PIs; group C: 5% of PIs)*

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## Appendix 1: CLEO® scale

### 1. Clinical impact

| Score | Impact | Definition: The clinical impact is evaluated according to the most likely case expected, not the worst / best case |
|---|---|---|
| **-1C** | **Negative** | The PI can lead to adverse outcomes on clinical status, knowledge, satisfaction, patient adherence and/or quality of life of the patient. |
| **0C** | **Null** | The PI can have no influence on the patient regarding the clinical status, knowledge, satisfaction, patient adherence and or quality of life of the patient. |
| **1C** | **Minor** | The PI can improve knowledge, satisfaction, medication adherence and/or quality of life OR the PI can prevent harm that does not require monitoring/treatment. |
| **2C** | **Moderate** | The PI can prevent harm that requires further monitoring/treatment, but does not lead to or does not extend a hospital stay. |
| **3C** | **Major** | The PI can prevent harm which causes or lengthens a hospital stay OR causes permanent disability or handicap. |
| **4C** | **Avoids Fatality** | The PI can prevent an accident that potentially causes the need for intensive care or death of the patient. |
| **UND** | **Undetermined** | The available information does not allow to evaluate clinical impact. |

- The clinical impact is evaluated in terms of the benefit to the patient.
- Harm: alteration of physical and mental capacities arising from an accident or illness.
- Quality of life: physical function (autonomy, physical abilities, capacity to perform the tasks of daily life etc.), psychological (anxiety, depression, emotions etc.), social (relative to family environment, friends or professional contacts, engaging in personal relationships, participation in social and leisure activities etc.) and somatic (symptoms related to the disease).
- Monitoring: monitoring clinically relevant (physiological or psychological) variables, and/or biological parameters.
- Treatment: changing therapy or adding an additional medical / surgical treatment.

### 2. Economic impact

| Score | Impact | Definition |
|---|---|---|
| **-1E** | **Increase in cost** | The PI increases the cost of the drug treatment. |
| **0E** | **No change** | The PI does not change the cost of drug treatment. |
| **1E** | **Decrease in cost** | The PI cuts the cost of drug treatment. |
| **UND** | **Undetermined** | The available information does not allow to evaluate economic impact. |

- The cost of drug therapy contains two main elements:
  - o The cost of the drugs
  - o The cost of monitoring drug therapy (e.g., clinical monitoring, kinetics, biological monitoring etc.).
- The cost of drug therapy is based on the financial cost for the hospital.

### 3. Organizational impact

| Score | Impact | Definition |
|---|---|---|
| **-1O** | **Negative** | The PI reduces the quality of care. |
| **0O** | **Null** | The PI does not change the quality of care. |
| **1O** | **Positive** | The PI increases the quality of care. |
| **UND** | **Undetermined** | The available information does not allow to evaluate organizational impact. |

- The organizational impact is coded in terms of the **overall impact** on the quality of the care process from the **perspective of the health care providers** (e.g., time saving; improved security, knowledge or job satisfaction for nursing staff; facilitating tasks or teamwork, continuity of care etc.)



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# STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| **Title and Abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | |
| **Introduction** | | | |
| Background/Rationale | 2 | Explain the scientific background and rationale for the investigation being reported | |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | |
| **Methods** | | | |
| Study Design | 4 | Present key elements of study design early in the paper | |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br><br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br><br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br><br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | |

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| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| Data Sources/ Measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study Size | 10 | Explain how the study size was arrived at | |
| Quantitative Variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | |
| Statistical Methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br><br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br><br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive Data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | |
| Outcome Data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time | |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure | |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures | |



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| Section and Item | Item No. | Recommendation | Reported on Page No. |
|---|---|---|---|
| Main Results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other Analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key Results | 18 | Summarise key results with reference to study objectives | |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | |
| **Other Information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.**

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