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RESEARCH ARTICLE

# Non-adherence to Immunosuppressant after Lung Transplantation – A Common Risk Behavior

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**Abstract:**

***Background:***

After lung transplantation, life-long treatment with immunosuppressive medication is required to prevent rejection and graft loss but adherence to immunosuppressive treatment may be difficult for the lung recipient. Adherence is essential and non-adherence to immunosuppressive treatment can lead to graft loss and death.

***Objective:***

The aim of this cross-sectional study was to investigate the prevalence of non-adherence 1 to 5 years after lung transplantation in relation to symptom burden, health literacy, psychological well-being and relevant demographic variables.

***Methods:***

117 adult lung recipients, due for their annual follow-up 1-5 years after lung transplantation, participated. Four self-report instruments were used for assessment: the Basel Assessment of Adherence with Immunosuppressive Medication Scale, the Newest Vital Sign, the Psychological General Well-Being and the Organ Transplant Symptom and Wellbeing Instrument. Statistical analysis was performed.

***Results:***

Thirty percent of the lung recipients were non-adherent. The most common non-adherence dimension was not taking a dose (43%) and not being punctual with the regimen (80%). Of those working full time or part time, 43% were non-adherent (p=.032). A higher level of non-adherence was reported a long time after LuTx with the highest level at the 3-year follow-up.

***Conclusion:***

The level of non-adherence among lung recipients was high. The highest levels were found among those who had returned to work. Non-adherence increased with time after lung transplantation.

**Keywords:** Lung transplantation, Non-adherence, Symptoms, Health literacy, Well-being, Self-report instruments.

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|---|---|---|---|

## 1. INTRODUCTION

For patients with terminal vital organ failure such as heart, lungs, liver or kidneys, solid organ transplantation is a well-established treatment. A person's immune defense system reacts to all cells that are unfamiliar to that specific individual which includes transplanted organs. Therefore, organ transplantation requires life-long treatment with immunosuppressive medication to prevent graft rejection, graft loss and death. Adherence to treatment is challenging for all patients with life-long treatment and it is well known that adherence to immunosuppressive treatment may be difficult for organ transplant recipients. However, adherence is essential as non-adherence to immunosuppressive treatment can lead to severe consequences

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for transplanted persons. Late acute graft rejection and graft loss are associated with non-adherence to immunosuppressive drugs as well as the development of so-called donor-specific antibodies [1 - 5]. If a person develops donor-specific antibodies, the risk of graft rejection increases and it also makes it more difficult to find a suitable donor if re-transplantation is necessary [3, 4]. Studies on transplant recipients from North America show a higher level of non-adherence than studies from Europe [6]. Adherence can be defined as "the extent to which a person's behaviour (taking medications, following a recommended diet and/or executing life-style changes) corresponds with the agreed recommendations from a health care provider. Explanations for non-adherence to all forms of long-term treatment are complex and multifactorial. It involves patient and treatment regimen factors, as well as factors related to the health care system/ healthcare team and socio-economic factors. Patient related factors can be forgetfulness, complicated medication regimen or experiences of side-effects. Heath care system factors can be the kind of information given, continuity of care and frequency of follow-up visits. Socio-economic factors can be the patients' financial situation, poor social support, dysfunctional family situation or drug abuse [7]. It is common for patients on immunosuppressive therapy to experience high symptom levels related to the treatment, *e.g.* trembling hands, diarrhoea, changed body image or pain, with women being affected to a higher degree [8, 9]. This can result in decreased quality of life and may affect the level of adherence to treatment [10, 11]. A meta-analysis revealed that patients suffering from depression have a three times greater risk of non-adherence to medical treatment than patients without depression [12]. Furthermore, a person's ability to obtain, process and understand basic health information in order to make informed decisions about health behaviour, *i.e.*, health literacy [13] affects transplant outcomes [14].

Non-adherence to immunosuppressive treatment is complex, difficult to measure and there is no gold standard available, although self-reporting is generally considered to be an essential part of adherence assessment [15]. A recent systematic review including 30 relevant studies revealed that non-adherence to immunosuppressive medication after lung transplantation ranged from 2.3% to 72.2% [16]. None of the reviewed studies were conducted in a Scandinavian context. This study stems from the assumption that the factors identified in previous literature of importance for non-adherence are relevant also for Swedish lung recipients. Thus the aim of this study was to investigate the prevalence of non-adherence 1-5 years after lung transplantation in relation to relevant sociodemographic variables, health literacy, symptom burden and psychological well-being and in a Swedish context.

## 2. MATERIALS AND METHODS

This multicentre cross-sectional cohort study is a part of the Swedish national study entitled Self-Management After Thoracic Transplantation (SMATT). The inclusion criteria were; adult (>18 yrs) lung recipients due for an annual follow-up 1-5 years after lung transplantation (LuTx) at either of the two thoracic transplant centres in Sweden (Lund & Gothenburg), Swedish speaking, mentally lucid, not hospitalized and without on-going rejection treatment with high dose steroids. The study was performed between 2014 and 2015, at that time 204 lung recipients were due for the yearly follow-up, of whom 117 (57%) fulfilled the inclusion criteria, agreed to participate and were included in the study. The reasons for non-participation in the study were; poor health status, language barriers, declining to participate for unknown reasons and staff shortages that resulted in lack of time to assess persons for inclusion in the study.

The Regional Ethical Review Board in Lund, Sweden granted permission to perform this study (D-nr 2014-124). All participants gave their written informed consent. The information provided by the participants was kept confidential and stored by the researchers in accordance with the Swedish personal data act; PuL-[1998:204].

### 2.1. The Instruments and Data Collection

Data collection was done when the study participants were attending their routine 1-5 years follow-up after LuTx. Four instruments were used in this study, two interview questionnaires, the Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS®) [17] and the Newest Vital Sign (NVS) [18] and two questionnaires for completion by the participants, the Psychological General Well-Being (PGWB) [19, 20] and the Organ Transplant Symptom and Wellbeing Instrument (OTSWI) [21].

The BAASIS®, a self-report instrument (the interview version) [17], was used for assessing adherence to immunosuppressive drugs. The BAASIS® is operationalised to measure four dimensions of adherence during the previous four weeks; taking (taking the prescribed immunosuppressive), timing (taking immunosuppressive every 12 hrs, +/- 2 hrs), drug holidays (skipping immunosuppressive > 24 hrs) and dose changing (changing from the prescribed dose). If the respondent reports non-adherence to any of the four dimensions, she/he is considered non-adherent [17]. The BAASIS has not been validated in the Swedish language but has been used in other transplant populations (Cronbach $\alpha = 0.7$) [18].

The health literacy level was assessed using the NVS operationalised to assess both numeric and word literacy. It has been shown to have good internal consistency (Cronbach $\alpha = 0.76$) [19]. The NVS has six short interview questions. Study participants were provided with a nutrition label and asked six questions to assess their health literacy level. The responses were recorded on a special score sheet, which also contained the correct answers. The health literacy level is based on the number of correct responses, where a score of 0-1 indicates low health literacy; 2-3 possibly limited health literacy and 4-6 adequate HL.

The interviews, *i.e.* BAASIS and NVS, were performed by either one of the two transplant nurses working at the two transplant outpatient-clinics. These four nurses were trained in how to use the instruments prior to the study. The questions were posed to the LuTx recipients at their 1-5 year follow-up visit at the transplant outpatient-clinic by the transplant nurse in a non-threatening, non-judgmental way.

The Swedish version of the PGWB instrument was used to

measure psychological well-being and distress [20, 21]. The instrument contains 22 items, which is operationalised into six dimensions: *anxiety*, *depressed mood*, *positive well-being*, *self-control*, *general health* and *vitality*. Inter-item correlation values range from 0.53-0.79 and Cronbach's Alpha ranges from 0.61-0.89. For each of the 22 questions, response was given on a six-point Likert-scale with different response alternatives for every question. The PGWB total sum-score was 132, while higher scores indicate better psychological well-being. A normal sum-score is in the range of 100-105. The sum score was dichotomized as a cut off between low (0-100) and good physiological well-being (101- 132).

The OTSWI was developed to measure symptom prevalence, symptom distress and transplant specific well-being after organ transplantation [22]. It was used to assess transplant specific symptoms and well-being. It measures distress from eight dimensions and 20 transplant specific symptoms. The distress is assessed on a five-point Likert-scale: "not at all" (0), "a little" (1), "somewhat" (2), "quite a bit" (3), and "very much" (4). The OTSWI has a sum score of 0-80, where lower scores indicate higher well-being. Item scale correlations ranged from 0.66 -0.98 and the Cronbach's alpha coefficient was satisfactory for all scales, ranging from 0.81-0.92.

The PGWB and OTSWI instruments are self-reported questionnaires, which were filled in by the participants and returned at the routine follow-up appointment. At this time point, they also filled in an author constructed questionnaire with demographic variables regarding age, sex, social situation, educational level and ability to work.

### 2.2. Data Analysis

The SPSS Statistics (SPSS Inc., IBM Corporation, Armonk, NY, USA) was used for analysing data, which were mostly ordinal. Ordered category data are presented with medians and percentiles ($P_{25}$, $P_{75}$). Values of $P < 0.05$ (two-tailed) were considered statistically significant. Age was dichotomised into two groups, younger and older than 50 years. The analysis was performed step-wise as follows exploring proportions one to five years after LuTx followed by proportional differences between unpaired groups which were analysed with Chi-Square test. Differences in health literacy, symptom burden and psychological well-being between adherent and non-adherent recipients were explored with Mann Witney U test. Finally, differences between three unpaired groups, *i.e.* educational level, were analysed with Kruskal Wallis test.

## 3. RESULTS

117 participants were due for their annual follow-up as follows; 1 year (n=35), 2 years (n=28), 3 years (n=23), 4 years (n=20) and 5 years (n=11). The demographics of the study participants are presented in Table **1** and indications for LuTx are presented in Table **2**, where the two most prevalent indications for transplantation were chronic obstructive pulmonary disease and lung fibrosis. The median age was 56.5 years and the mean age was 53.5 years (SD=12.5 years), ranging from 18-74 years. Sex was equally distributed (59 women and 58 men) and 64% of the participants were married.

**Table 1. Demographic characteristics at follow-up 1-5 years after lung transplantation.**

| – | Follow-up Time after Lung Transplantation | | | | | |
|---|---|---|---|---|---|---|
| | 1 year (n=35) | 2 years (n=28) | 3 years (n=23) | 4 years (n=20) | 5 years (n=11) | All (n=117) |
| **Variable** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** |
| **Gender** | | | | | | |
| Female | 18(51.4) | 11(39.3) | 12(52.2) | 11(55.0) | 7(63.6) | 59(50.4) |
| Male | 17(48.6) | 17(60.7) | 11(47.8) | 9(45.0) | 4(36.4) | 58(49.6) |
| **Age** | | | | | | |
| ≤49 years | 8(22.9) | 10(35.7) | 3(13.0) | 6(30.0) | 5(45.5) | 32(27.4) |
| ≥50 years, | 27(77.1) | 18(64.3) | 20(87.0) | 14(70.0) | 6(54.5) | 85(72.6) |
| Median (IQR) | 57[50,64] | 54[41,63] | 57[51,62] | 59[44,66] | 58 [37,66] | 57[47,63] |
| **Marital Status** | | | | | | |
| Married or cohabitant | 19(61.3) | 21(75.0) | 14(63.6) | 17(85.0) | 4(40.0) | 75(67.6) |
| Widowed, single | 12(38.7) | 7(25.0) | 8(36.4) | 3(15.0) | 6(60.0) | 36(32.4) |
| Missing | 4 | 0 | 1 | 0 | 1 | 6 |
| **Living Situation** | | | | | | |
| Living with children | 10(32.3) | 8(28.6) | 5(23.8) | 2(10.0) | 2(20.0) | 27(24.5) |
| Living without children | 18(58.0) | 15(53.6) | 13(61.9) | 16(80.0) | 7(70.0) | 69(62.7) |
| Other | 3(9.7) | 5(17.8) | 3(14.3) | 2(10.0) | 1(10.0) | 14(12.7) |
| Missing | 4 | 0 | 2 | 0 | 1 | 7 |
| **Education** | | | | | | |
| Primary | 5(16.2) | 9(32.2) | 5(22.7) | 5(25.0) | 1(10) | 25(22.5) |
| Secondary/Vocational education | 18(58.0) | 13(46.4) | 12(54.6) | 12(60.0) | 4(40) | 59(53.1) |
| University | 8(25.8) | 6(21.4) | 5(22.7) | 3(15.0) | 5(50) | 27(24.4) |

| – | Follow-up Time after Lung Transplantation | | | | | |
|---|---|---|---|---|---|---|
| | **1 year (n=35)** | **2 years (n=28)** | **3 years (n=23)** | **4 years (n=20)** | **5 years (n=11)** | **All (n=117)** |
| **Variable** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** | **n(%)** |
| Missing | 4 | 0 | 1 | 0 | 1 | 6 |
| **Perceived Ability to Work** | | | | | | |
| Unable to work | 18(60.0) | 12(42.9) | 10(45.4) | 13(65.0) | 4(40.0) | 57(51.8) |
| Full time<br>Part time | 4(13.3)<br>8(26.7) | 9(32.1)<br>7(25.0) | 6(27.3)<br>6(27.3) | 3(15.0)<br>4(20.0) | 4(40.0)<br>2(20.0) | 26(23.6)<br>27(24.6) |
| Missing | 5 | 0 | 1 | 0 | 1 | 7 |

IQR= Inter Quartile Range

The BAASIS showed that 30% of the lung recipients were non-adherent (35/117). The non-adherence regarding taking was 43% (15/35) and the most frequent non-adherence behaviour was timing (punctuality), 80% (28/35). Ten participants reported more than one non-adherence dimension (29%), where the most common combination was taking and timing.

Of those working full or part-time 43% were non-adherent. Lung recipients able to work full or part-time were significantly (p=0.032) less adherent than those unable to work (Table **3**).

No differences in adherence were found when comparing two or more independent groups, *i.e.*, sex, patients older or younger than 50 years, marital status, educational level and ability to work.

The prevalence of non-adherence differed significantly between the follow-up years (p=0.047). Non-adherence was 14% at 1 year follow-up and 52% at the 3 year follow-up. It was approximately 30% at the 2, 4 and 5 year follow-ups (Table **4**).

Health literacy was similar in the adherent and non-adherent group (p=0.628). Eight percent in the adherent group and 3% in the non-adherent group scored 0-1 on the NVS indicating low health literacy, while 14% in the adherent group and 17% in the non-adherent group scored 2-3 indicating possibly limited health literacy. A total of 78% in the adherent group and 80% in the non-adherent group scored 4-6, suggesting an adequate health literacy level in both the adherent and the non-adherent groups.

The OTSWI sum score ranged from 0-57 with a mean of 16.8 (SD 12.37) and 30% of the study group scored under 10, indicating a high level of well-being. The symptom burden was greater in the non-adherent group regarding low appetite (p=0.012) and diarrhoea (p=0.007).

The PGWB sum score was dichotomized to low or good psychological well-being where 44% of the adherent group and 40% of the non-adherent group rated low psychological general well-being, which difference was not significant (p=0.779). No relationships were found between adherence and overall psychological well-being, age or health literacy.

**Table 2. Indications for transplantation, type of lung transplant and immunosuppressive medications, reported by the study participants (n= 117).**

| **Indication for Lung Transplantation** | **n (%)** |
|---|---|
| Chronic obstructive pulmonary disease | 29 (25) |
| Lung fibrosis | 24 (21) |
| Cystic fibrosis | 19 (16) |
| Alpha 1- antitrypsin deficiency | 19 (16) |
| Pulmonary arterial hypertension | 7 (6) |
| Emphysema | 4 (3) |
| Bronchiectasis | 3 (3) |
| Other* | 12 (10) |
| **Type of Transplantation** | **n= * (%)** |
| Double lungs | 98 (84) |
| Single lung | 18 (16) |
| **Immunosuppression** | **n (%) **** |
| Mycophenolate mofetil | 79 (75) |
| Steroids | 63 (59) |
| Cyclosporine | 61 (58) |
| Tacrolimus | 45 (42) |
| Azathioprine | 12 (11) |
| Other | 34 (32) |

*Information about one patient is missing, as are data regarding the type of graft in one patient, n=116. ** Missing data on 11 patients, n= 106. All patients took more than one immunosuppressive type of medication.

**Table 3. Factors related to non-adherence to immunosuppressive medication.**

| Variable | Total | Non-adherent n(%) | Adherent n(%) | $\chi^2$ test *p* value |
|---|---|---|---|---|
| **Gender** | 117 | – | – | 0.550 |
| Male | 58 | 19(32.8) | 39(67.2) | |
| Female | 59 | 16(27.1) | 43(72.9) | |
| **Age** | | | | 0.510 |
| 18-49 y/o | 32 | 11(34.4) | 21(65.6) | |
| 50-74 y/o | 85 | 24(28.2) | 61(71.8) | |
| **Marital status** | 111 | – | – | 0.070 |
| Married or cohabitant | 75 | 20(26.7) | 55(73.3) | |
| Living alone | 36 | 15(41.7) | 21(58.3) | |
| **Educational level** | 111 | – | – | 0.690 |
| Elementary level | 25 | 6(24.0) | 19(76.0) | |
| Secondary/vocational level | 59 | 21(35.6) | 38(64.4) | |
| University level | 27 | 8(29.6) | 19(70.4) | |
| **Ability to work** | 110 | – | – | 0.008 |
| Working full time or part time | 53 | 23(43.4) | 30(56.6) | |
| Unable to work | 57 | 12(21.0) | 45(79.0) | |

**Table 4. This table shows the distribution of adherence and non-adherence among 117 lung recipients with regard to the year of follow-up.**

| Follow-Up Year | Adherent n(%) | Non-adherent n(%) | Total n(%) |
|---|---|---|---|
| 1 | 30(85.7) | 5(14.3) | 35(29.9) |
| 2 | 19(67.9) | 9(32.1) | 28(23.9) |
| 3 | 11(47.8) | 12(52.2) | 23(19.7) |
| 4 | 14(70.0) | 6(30.0) | 20(17.1) |
| 5 | 8(72.7) | 3(27.3) | 11(9.4) |
| Total | 82(70.0) | 35(30.0) | 117(100.0) |

## 4. DISCUSSION

The key finding of this study was that the level of non-adherence among lung recipients was high. The highest levels were found among those who had returned to work. A higher level of non-adherence was reported a long time after LuTx with the highest level at the 3 year follow-up.

When screening with the BAASIS, the level of non-adherence among the lung recipients was surprisingly high at 30%, which is worrying. A high level of non-adherence (27%) measured with the BAASIS after LuTx was also shown by Drick *et al.* [23]. In contrast, Bosma and colleagues found that only 8% of the lung recipients were non-adherent, although in that study the instrument BAASIS was not used to measure non-adherence *i.e.* other instrument of measuring adherence was used, which makes it difficult to compare studies [24].

An established goal after organ transplantation is that the recipient returns to work within 24 months [25, 26]. An important finding in the present study was the difference in adherence among the persons who had returned to work compared to those who were not working, where the persons working had a significantly higher level of non-adherence. Of those working full or part-time, 43% were non-adherent. Based on our clinical experience, if you are busy with your normal everyday life and feel healthy, it is easy to forget that you have a condition that requires continuous medication. This indicates that persons in full or part-time employment need more self-management support from the health care team to develop medication routines suitable for their everyday life. We suggest that the most appropriate approach is person-centred care with an individual assessment of adherence, work situation and social situation on a regular basis.

Non-adherence increased with time since transplantation and was 14% at the 1 year follow-up, peaking to 52% at the 3 year follow-up and remained at 30% at the 5 year follow-up.

That non-adherence increases over time after transplantation has also been shown by others [23, 27]. An explanation can be that over time when you experience well-being it may be difficult to comprehend that the medication is still needed. These results indicate that regular screening of adherence and long-term follow-up after LuTx are of great importance. Therefore, individualized follow-up after LuTx is needed. A suggestion to achieve this is digitalized follow-up in the form of frequent reminders about medication intake as a complement to face to face follow-up visits.

There is also a need to transform the follow-up after LuTx from the medical to the health promotion perspective through

self-management support [28]. The medical perspective presupposes a form of practice that aligns with expectations that patients follow and comply with medical directions in a manner that acknowledges professional power and legitimacy [29, 30]. The medical perspective involves a modus operandi that emphasizes treatment guided by an expert and depicts patients as needing help and health professionals as legitimate experts in ensuring that this help is provided [31]. In contrast, health promotion involves both person-oriented and group-oriented dimensions [32], suggesting that in health promotion the person is seen as part of her/his social context. Health promotion is aimed at empowering individuals to take control of their health, which is depicted as a process of enabling persons to take increased responsibility for their own health and well-being [28]. Thus, providing health promotion to lung recipients means helping them by addressing the non-medical factors of their health, *i.e.*, acknowledging patients' knowledge of their own health. Transplant professionals must change their way of thinking and frames of reference when meeting lung recipients and focus on well-being and health rather than symptoms and limitations [9]. The LuTx recipient is the expert on her/his everyday life and can thus provide suggestions and interventions that will most likely facilitate adherence.

Previously, there have been numerous explanations behind non-adherence to long-term therapy such as the Health Belief Model [33], the Theory of Planned Behavior [34], the Social Learning Theory [35] and the Necessity-Concerns Framework [36]. These models suggest that non-adherence is largely intentional, indicating that patients after assessing pros and cons make a rational choice not to adhere. However, it has also been suggested that non-adherence could be unintentional [37]. Unintentional non-adherence does not depend on the choice of the patient but rather on factors such as poor understanding of the prescription, difficulty to access the prescribed medication, intervention of the patient's habits, lack of memory, defence mechanisms or simply irrationality [38]. Our understanding is that the high level of non-adherence in our study stems from mainly unintentional behaviour due to complicated logistics in everyday life.

Reach *et al.* [39] tested the hypothesis that adherence to medication in chronic diseases, *e.g.* diabetes is linked to time projection. This is defined as consisting of three psychological constructs; a) patience/impatience, b) greater or lesser ability to imagine remote future events (size of temporal horizon) and c) perception of the degree of physical similarity of current self to future self. They suggest that disruption in the time projection plays a role in both intentional and unintentional non-adherence [39]. Thus, some LuTx recipients with disruption in time projection may prefer either as a personal choice, or under pressure of external elements, such as social adaptation or demands of going back to work to prioritise immediate rewards *i.e.* making a choice not to adhere. The study by Reach *et al.* [39], onpatients with diabetes reported that there was a unique association between adherence to medication and patients' time projection. The ability to imagine oneself physically in the future was linked to adherence. Transferred to lung recipients, the persons who have the ability to view themselves as long-term survivors might be better off, while impatient persons need more short-term rewards for adherence to be motivated instead of advised on how to avoid long-term complications from their LuTx. This is an interesting hypothesis that needs further exploration.

To increase adherence to immunosuppressant drugs after LuTx we suggest the following:

- Special focus on those who have returned to work, which is an important part of their social context.
- Individualized and tailored self-management support based on the social situation and workload.
- Provide digital tools suitable for each person's needs.
- If necessary, establish a firm nurse-patient relationship based on a partnership and a contract regarding acceptable adherence behaviour.
- Increase the accessibility of care by means of e-health or mobile-health solutions, which should be considered an option when transplanted persons live far away from the out-patient clinic as well as for persons in full or part-time employment who may have limited time for hospital visits.
- All this requires staff continuity in order to establish trustful caring relationships in the outpatient clinics focusing on health promotion.

Limitations of this study are the cross-sectional design *i.e.* it is only a snapshot at a certain time-point and the study participants were not followed over time. There is also the risk of recall bias when using instruments asking for data during a time period. Health literacy was measured with the instrument NVS, which is not specifically developed for the transplant recipients. Splitting the study population in years of follow-up makes each group small in numbers.

## CONCLUSION

In conclusion, this study shows that non-adherence to immunosuppressant among lung recipients was high, with the highest non-adherence levels among those who had returned to work. The most frequent non-adherence behaviours were taking and timing, which are usually associated with forgetfulness and routines. A higher level of non-adherence was also reported after a longer period of time after LuTx.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| **LuTx** | = | Lung Transplantation |
| **BAASIS** | = | The Basel Assessment of Adherence with Immunosuppressive Medication Scale |
| **NVS** | = | The Newest Vital Sign |
| **PGWB** | = | Psychological General Well-Being |
| **OTSWI** | = | The Organ Transplant Symptom and Wellbeing Instrument |

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Regional Ethical Review Board in Lund, Sweden granted permission to perform this study (D-nr 2014-124).

## HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research

procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

## CONSENT FOR PUBLICATION

All participants gave their written informed consent.

## AVAILABILITY OF DATA AND MATERIALS

There is no webpage from where the data can be retrieved. However, calculations and raw data can be retrieved upon request.

## FUNDING

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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