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Original Article

Therapeutic needs in solid organ transplant recipients: The American Society of Transplantation patient survey

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ABSTRACT

The American Society of Transplantation commissioned a survey assessing transplant recipients' perceptions of unmet immunosuppressant needs. Topics included medication side effects, treatment burden, health-related quality of life, adherence, self-efficacy, costs, trust, and discrimination; 10 091 responses were included (9543 adults, 548 pediatric respondents) representing 232 transplant centers. Respondents were a mean of 6.6 years posttransplant and were well-represented across age, gender, race, ethnicity, organ, employment, insurance, and immunosuppression. Nearly all (92%) respondents reported at least 1 side effect (median of 3); most side effects occurred "often" or "always." The majority (54%) of side effects were rated as having a "moderate" or "great deal" of impact on daily life. Side effects with the greatest daily burden included skin cancer, pain/neuropathy, skin issues, kidney disease, memory/brain fog, diabetes, cancer, and hypertension. Fatigue, headache, insomnia, tremors, and mood/depression/anxiety were the most selected side effects. Health-related quality of life was rated as "fair" to "good." Trust in providers, self-efficacy, and medication adherence were rated highly, though 25% reported

Abbreviations: AST, American Society of Transplantation; HRQoL, health-related quality of life; IQR, interquartile range; mTOR, mammalian target of rapamycin; SRTR, Scientific Registry of Transplant Recipients.

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skipping doses due to side effects, and 40% skipped due to costs. The findings demonstrate that side effects are nearly universally experienced and have a major burden on daily life. Immunosuppression induces a heavy toll on transplant recipients; there is an urgent need for new treatments to address these unmet needs.

1. Introduction

Organ transplantation is the preferred treatment for end-stage organ failure but remains a suboptimal and time-limited intervention that often fails to fully restore lasting health, vitality, and daily functioning. For instance, the median survival for kidney allografts from deceased donors is approximately 11.7 years,[1] and transplant recipients die at a much higher rate when compared to the age-matched general US population.[2] Although transplantation typically enhances health-related quality of life (HRQoL),[3] recipients commonly contend with a wide range of distressing symptoms and adverse effects or comorbidities exacerbated by immunosuppression regimens.[4] Moreover, a considerable number of kidney, heart, lung, and liver transplant recipients remain functionally impaired after transplantation.[5,6] Such impairment is largely driven by the burdensome and sometimes severe side effects of immunosuppression regimens and the limited therapeutic interventions available to mitigate these adverse effects.[7,8]

Since 2011, no new immunosuppressive agents have received approval for use in solid organ transplantation, leaving most regimens virtually unchanged over the past 15 years.[9,10] Historically, drug development in transplantation has prioritized reducing 1-year acute rejection and graft loss, leading to potent immunosuppression that provides good short-term graft outcomes. However, for many recipients, these therapies substitute the fatal consequences of organ failure with new chronic conditions—such as hypertension, diabetes, and chronic kidney disease—that cause debilitating side effects and reduce HRQoL, limit functional independence (eg, ability to work or attend to all family needs), and reduce long-term survival. To make matters worse, the treatment of these chronic conditions further increases the already significant medication burden imposed by lifelong immunosuppression.

The Food and Drug Administration and European Medicines Agency have historically approved new transplant immunosuppressants based on clinician-reported outcome measures that are intended to reflect how a patient feels, functions, or survives. Yet, in the transplant context, the therapies used to prevent rejection counterintuitively commonly cause severe and irreversible toxicities that impact the feel, function, and survival paradigm but are not part of the primary trial endpoints. Considering these issues, the American Society of Transplantation (AST) Board of Directors endorsed and funded the design and wide dissemination of a survey to be conducted among a representative cohort of transplant recipients and caregivers. The motivation to conduct this survey was to gain a clear and comprehensive assessment of transplant recipient perceptions of current immunosuppressive therapy use and unmet needs. Insights gained are intended to address these needs to spur innovative initiatives. The objective of this study is to provide the overarching findings of this completed survey, focusing on the burdens associated with contemporary immunosuppression used in transplant.[11-14]

2. Materials and methods

2.1. Study design and participants

This was a cross-sectional web-based survey of pediatric and adult solid organ transplant recipients to assess patient perceptions of their immunosuppressive therapies. Participants were recruited, either directly or through transplant professionals affiliated with AST, if they met the following criteria: (1) self-identified or identified by parent/guardian as an organ transplant recipient, and (2) legal adult, based on residence criteria ($\geq$18 years of age, with the following exceptions: $\geq$19 years in Nebraska and Alabama, and $\geq$21 years in Mississippi). Respondents were excluded if they were not based in the US or Canada, did not provide informed consent to taking and completing the survey (by opening the link, checking a box indicating consent, and completing the survey), or provided inaccurate or fake responses, based on a predeveloped survey validation system. The system was set up to remove survey responses that were likely from automated chatbots, were clearly false, or were unlikely to provide relevant information. This included reCAPTCHA validation, validation of age versus transplant year, validation of organ transplant type (match checkbox and write-in), validation of a realistic immunosuppression regimen, and a timing validation system using metadata based on how quickly survey components were completed. Graft failure or retransplant status was not an exclusion criterion. Advarra central institutional review board provided approval and oversight for all study-related activities (Pro00071337).

2.2. Survey development and dissemination

Details about the survey development and dissemination can be found in the supplementary material and in a previous publication.[11] In brief, the survey was developed over an 18-month iterative process involving transplant professionals, transplant recipients, and family members. After the AST survey endorsement, a group of 8 experts in survey development and clinical transplantation was convened into a task force and began biweekly meetings.[11] Questions and responses to sociodemographic variables were developed to align with either the United Network of Organ Sharing Tiedi forms or U.S. Census questionnaires, when applicable. Previously developed and

validated surveys were identified that would meet study objectives and cover the 18 topics. Supplementary Table 1 displays 18 topics, item numbers, question types, and supporting literature.

The final survey was opened and launched at the American Transplant Congress on June 4, 2023, and remained open until September 30, 2024. The goal was to obtain at least 10 000 valid responses from a representative adult and pediatric solid organ transplant population. Survey dissemination and recruitment efforts were used by AST staff, professional members, leaders, and affiliates, and are listed in Supplementary Table 2. The complete survey is available in Supplementary Methods.

2.3. Data collection

Detailed baseline demographics, immunosuppression regimens, and transplant characteristics were collected, which matched United Network of Organ Sharing Tiedi or U.S. Census Bureau forms, when possible. The survey was focused on maintenance immunosuppression, not induction or rejection treatments. The survey covered the ranking of the 18 immunosuppressant-related topics identified by the brainstorming sessions. This included frequency, severity, and overall life impact of immunosuppressant side effects, HRQoL, treatment burden, self-care, and concerns related to rejection, loss of graft function, infection, and cancer. Topics also included frequency and causes of immunosuppressant medication nonadherence, confidence in managing complex medication regimens, trust in the transplant care team, and challenges related to language, communication, and discrimination in health care.

2.4. Statistical analysis

Standard descriptive statistics were used to summarize the data and report central tendencies, including percentages for categorical data and mean, median, standard deviation, and interquartile ranges (IQR) for continuous and ordinal data (Likert scales).

To inform the representativeness of the survey respondents, the demographics of incident transplant recipients reported in the Scientific Registry of Transplant Recipients (SRTR) between 2015 and 2024 were compared to the survey respondents. The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, U. S. Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors.[15]

Margin of error was estimated using the following formula: 1.96 $\times$ (sqrt [{p $\times$ (1-p)}/n]); where p is the proportion of the survey numbers (10 091 participants in the final analytical data set) to 10-year SRTR (393 064) N, and n is the survey sample size. Inferential statistical analyses included univariate comparisons with either the Student's t-test, Wilcoxon rank sum, chi-square, or Fisher exact test based on data type and distribution. Multivariable analyses were used to develop a single measure of side effect burden and assess the impact of sociodemographics on this burden measure. Item response theory (Proc IRT), and factor analysis (Proc Factor) were used to develop the single side effect burden measure. The models included the 26 side effect frequencies and severities (52 variables), each on an ordinal Likert scale of 0 to 5. After reviewing these models, we generated the theta (Θ) from the IRT for each respondent and utilized it as the best single measure of side effect burden. However, Θ was highly correlated with both the factor analysis burden output ($R^2 = 0.895$) and a calculated burden measure (frequency $\times$ severity) for the 26 side effects ($R^2 = 0.850$). Following this step, we used a generalized linear model (Proc genmod) to assess the impact of baseline sociodemographics on side effect burden, with a log link and gamma distribution as the best fit for the data. We used Microsoft Excel (Microsoft Corp, Seattle, WA), SPSS version 28.0 (IBM Corp, Armonk, NY), and SAS version 9.4 (SAS Institute, Cary, NC) to conduct statistical analyses.

3. Results

3.1. Study cohort and participants' baseline characteristics

A total of 14 723 survey responses were received. Of these, 1360 (9.2%) were excluded for being from internet protocol addresses outside the US or Canada, 1620 (11.0%) were excluded for having a year of birth that was later than transplant year, 1251 (8.5%) were excluded for unrealistic immunosuppression regimen (2 concurrent calcineurin inhibitors, mammalian target of rapamycin [mTOR] inhibitors or both mycophenolic acid and mycophenolate mofetil), 289 (2.0%) were excluded due to not completing the fill in the blank question on type of organ transplant correctly, and 112 (0.8%) were excluded for being flagged for rapid completion by the web-based system (<3 minutes). Thus, 10 091 (68.5%) validated responses remained in the final analytical cohort, of which 9543 (94.6%) were from adults and 548 (5.4%) were from pediatric respondents (Fig. 1).

Respondent demographic characteristics are displayed in Table 1, with stratification between adults and pediatric respondents. The mean age for the overall cohort was 47 years (49 years in adults, 12 years in pediatric respondents), and respondents were an average of 6.6 years posttransplant. Approximately 50% were male, 79% White, 15% African American and 12% Hispanic/Latino/a; 46% were kidney recipients, followed by liver (23%), heart (12%), lung (10%), pancreas (5%), intestine (3%), and vascular composite (2%). Most adults had education levels above high school, with a good representation of participants who were working, retired, or those with disabilities. Most adults were married (68%), and most had private (52%), Medicare (52%), or Medicaid (21%) insurance. Pediatric respondents tended to have more racial and ethnic diversity, more heart and lung recipients, and more Medicaid insurance use. Supplementary Table 3 displays additional demographics (citizenship and primary language). Current and past immunosuppression regimens are displayed in Supplementary Table 4. Most (79%) reported that they were

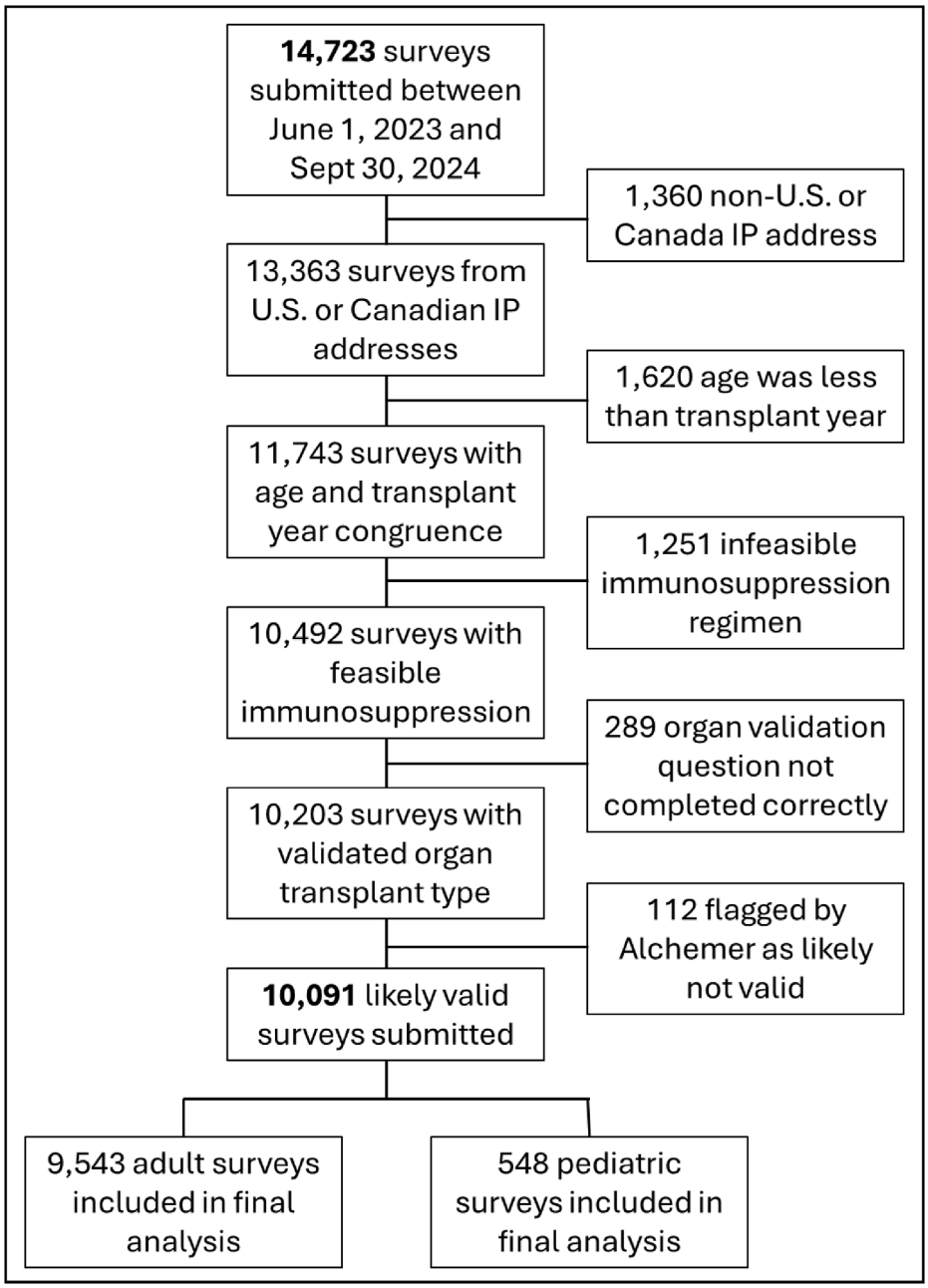

Figure 1. Study cohort creation and key exclusion reasons with numbers.

receiving a calcineurin inhibitor (64% tacrolimus, 15% cyclosporine), 53% a mycophenolate product, and 42% reported that they were receiving prednisone. Use of belatacept, mTOR therapy, and other agents (mainly azathioprine) was reported in 4% to 17% of the participants. Pediatric respondents tended to have higher reported use of cyclosporine and sirolimus, and lower use of tacrolimus, as compared to adults. Notably, 25% of participants reported having never changed their immunosuppressant regimen.

We compared survey participants' demographics to the past 10 years of available SRTR data (2015 to 2024, Supplementary Table 5). The survey participants represented 2.6% of the 10-year SRTR transplant patients, leading to a survey margin of error of ±0.3% for overall categorical data (±0.3% for adults and ±1.4% for children). As compared to the SRTR, the survey participants' mean age was slightly younger in adults (49 vs 53 years) and older in children (12 vs 8 years). Organ transplant type for both adults and children was similar to the SRTR data. Survey participants were slightly overrepresented in female gender and White race. Education and insurance status were well-represented in survey participants, as compared to SRTR patients.

3.2. List of constructs and ranking of importance

The 18 topics and rankings of importance are displayed in Figure 2. The results are skewed in favor of all topics being ranked as important to very important. All but 1 topic had a

Table 1
Baseline characteristics of all respondents, also stratified by adults and pediatric respondents.

Respondent characteristics	All participants (n = 10 091)	Adults (n = 9543)	Children (n = 548)
Mean age ± SD (y)	47.0 ± 18.2	49.0 ± 16.5	12.1 ± 5.0
Mean years posttransplant (±SD)	6.6 ± 6.8	6.6 ± 6.9	3.9 ± 3.2
Organ transplant[a]			
Kidney	4990 (45.6%)	4797 (46.3%)	193 (32.6%)
Liver	2553 (23.3%)	2439 (23.6%)	114 (19.3%)
Heart	1341 (12.3%)	1230 (11.9%)	111 (18.8%)
Lung	1101 (10.1%)	1029 (9.9%)	72 (12.2%)
Pancreas	495 (4.5%)	463 (4.5%)	32 (5.4%)
Intestine	306 (2.8%)	262 (2.5%)	44 (7.4%)
Vascular composite	160 (1.5%)	134 (1.3%)	26 (4.4%)
gender			
Male	5022 (49.8%)	4703 (49.3%)	319 (58.2%)
Female	5004 (49.6%)	4777 (50.1%)	227 (41.4%)
Other	65 (0.6%)	63 (0.7%)	2 (0.4%)
Race[b]			
White	7977 (79.1%)	7572 (79.3%)	405 (73.9%)
African American	1504 (14.9%)	1399 (14.7%)	105 (19.2%)
Asian	201 (2.0%)	189 (2.0%)	12 (2.2%)
Native American/Alaska Native	198 (2.0%)	180 (1.9%)	18 (3.3%)
Pacific Islander/Filipino	68 (0.7%)	60 (0.6%)	8 (1.5%)
Asian Indian	43 (0.4%)	40 (0.4%)	3 (0.5%)
Multiracial	159 (1.6%)	145 (1.5%)	14 (2.6%)
Other	176 (1.7%)	170 (1.8%)	6 (1.1%)
Ethnicity			
Latinx	1163 (11.5%)	1037 (10.9%)	126 (23.0%)
Mexican, Mexican American, or Chicano	684 (6.8%)	596 (6.2%)	88 (16.1%)
Puerto Rican	106 (1.1%)	99 (1.0%)	7 (1.3%)
Cuban	78 (0.8%)	71 (0.7%)	7 (1.3%)
Another Hispanic, Latino, or Spanish	293 (2.9%)	268 (2.8%)	25 (4.6%)
Highest education (missing = 11)			
Not enrolled in school yet	22 (0.2%)	1 (0.0%)	21 (3.8%)
Daycare/pre-K	30 (0.3%)	0 (0.0%)	30 (5.5%)
Grade school (K-8)	246 (2.4%)	57 (0.6%)	189 (34.5%)
High school (9-12) or GED	1379 (13.7%)	1180 (12.4%)	199 (36.3%)
Some college/technical school	2796 (27.7%)	2734 (28.6%)	62 (11.3%)
Associate/bachelor's degree	3850 (38.2%)	3812 (39.9%)	38 (6.9%)
Postgraduate degree	1757 (17.4%)	1748 (18.3%)	9 (1.6%)
Current employment (missing = 9)			
Working full-time	3649 (36.2%)	3569 (37.4%)	80 (14.6%)

(*continued on next page*)

Table 1 (*continued*)

Respondent characteristics	All participants (n = 10 091)	Adults (n = 9543)	Children (n = 548)
Working part-time	1577 (15.6%)	1518 (15.9%)	59 (10.8%)
Retired	2139 (21.2%)	2130 (22.3%)	9 (1.6%)
Not working due to illness or disability	1708 (16.9%)	1687 (17.7%)	21 (3.8%)
Not working by choice	333 (3.3%)	304 (3.2%)	29 (5.3%)
Homemaker	114 (1.1%)	114 (1.2%)	0 (0.0%)
Not working, unable to find employment	143 (1.4%)	138 (1.4%)	5 (0.9%)
Student or child	419 (4.2%)	74 (0.8%)	345 (63.0%)
Insurance status[c]			
Private	5285 (52.4%)	5004 (52.4%)	281(51.3%)
Medicare	5248 (52.0%)	5093 (53.4%)	155 (28.3%)
Medicaid	2086 (20.7%)	1929 (20.2%)	157 (28.6%)
Military, Veterans, or Tricare	350 (3.5%)	310 (3.2%)	40 (7.3%)
Uninsured	124 (1.2%)	87 (0.9%)	37 (6.8%)
Current marital status (missing = 3)			
Married/partnered	6798 (67.4%)	6474 (67.8%)	324 (59.1%)[d]
Single	1933 (19.2%)	1875 (19.6%)	58 (10.6%)
Widowed	380 (3.8%)	374 (3.9%)	6 (1.1%)
Divorced	735 (7.3%)	717 (7.5%)	18 (3.3%)
Child	186 (1.8%)	44 (0.5%)	142 (25.9%)
Other	56 (0.6%)	56 (0.6%)	0 (0.0%)

GED, generalized educational development; K, kindergarten; SD, standard deviation.

[a] Participant could select more than 1 organ transplant.

[b] Participant could select more than 1 race.

[c] Participant could select more than 1 type of insurance.

[d] Likely represents parental marital status.

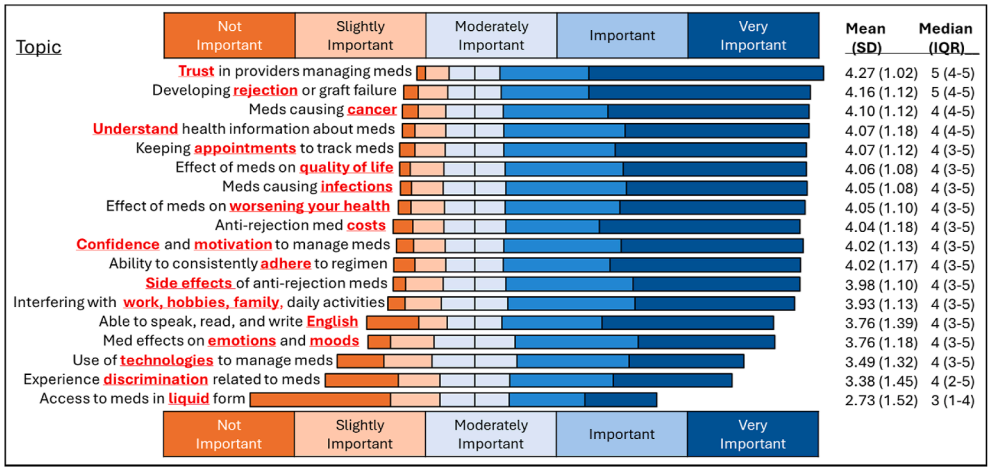

Figure 2. List of constructs and rankings based on level of importance as measured on a 5-point Likert scale. IQR, interquartile range; SD, standard deviation.

median ranking of important or very important. Only access to medications in liquid form was ranked as moderately important (median 3, IQR 1-4). The top 5 topics ranked in order of importance to transplant recipients included trust in the providers managing medications, development of rejection or graft failure, medications causing cancer, understanding health information

about medications, and keeping appointments to track medications.

3.3. Side effect frequency, severity, and overall burden

Respondents could select up to 23 side effects and write in 3 additional side effects; 92% reported at least 1 side effect, with a median of 3 (IQR 1-5) side effects reported per respondent. Of those selecting a side effect as present, 63% were reported as occurring "often" or "always," and 54% were rated as having a "moderate" or "great deal" of impact on daily life (see Supplementary Table 6). Fatigue, headaches, insomnia, tremors, and mood were the top 5 selected side effects (Fig. 3). The Likert scale rankings of side effect frequencies and severities are displayed in Figure 4. These were multiplied together to create a side effect burden (range of scores was from 1 to 25). Pain, fatigue, weight gain, muscle weakness, and low libido were the top 5 side effects with regard to burden. There was a total of 1135 write-in side effects. The most common write-in issues identified by respondents included skin cancer, pain/neuropathies, other cancers, kidney disease, hypertension, brain fog, and diabetes/hyperglycemia. These write-in side effects had a strong burden on respondents' lives, with a median frequency of 5 (always occurring [IQR 4-5]) and a median impact on daily life of 4 (moderate [IQR 3-5], see Fig. 5).

The association of respondent characteristics and immunosuppressant side effect burden is displayed in Table 2. The percent increase in side effect burden can be interpreted as the given variable leading to an estimated percent increase in side effect burden, if that variable were present versus absent. For example, those aged $\geq$60 years have an estimate of 23%, meaning their side effect burden was a mean of 23% higher than those $<$60 years old. The tacrolimus estimate was 26%, meaning those currently receiving tacrolimus had a 26% higher side effect burden than those not currently receiving tacrolimus. Unemployment due to disability, older age, higher education level, and White race all significantly increased the estimated side effect burden. Current immunosuppressants that significantly increased side effect burden included tacrolimus, mycophenolate products, and prednisone. Past immunosuppressant therapies that significantly increased side effect burden included tacrolimus, mTOR inhibitors, mycophenolate, prednisone, and other therapies (predominantly azathioprine). Variables not listed in Table 2 were not significantly associated with an increase or decrease in side effect burden (ie, current or past belatacept use).

3.4. HRQoL, treatment experience, rejection, graft loss, cancer, and infection

HRQoL was rated as a median of 3 ("good," IQR 3-4, Supplementary Table 7). One in 5 participants rated HRQoL "fair" or "poor," and 40% rated HRQoL as "very good" or "excellent." Physical health was rated slightly lower than mental health, but both had a median rating of 3 ("good"). Patient experience and self-management are displayed in Supplementary Table 8. The issues rated as the most concerning were developing an infection or cancer. Concerns about rejection and losing graft function were also rated highly. The most concerning issues related to self-care included interference with the ability to travel for work or vacation, interference with hobbies and daily activities, and being bothered by feeling dependent on others for health care needs. The issues of lowest concern included tracking medical appointments, monitoring health conditions, getting appointments, and keeping appointments with different health care providers.

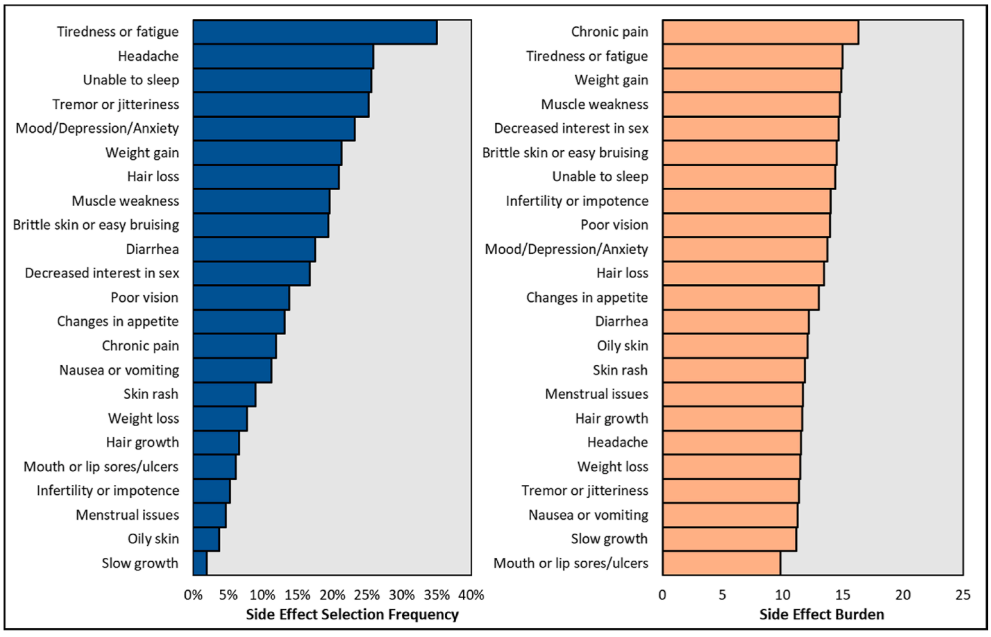

Figure 3. Side effect selection frequency (left panel) and overall burden (right panel) ordered from most common/burdensome to least common/burdensome.

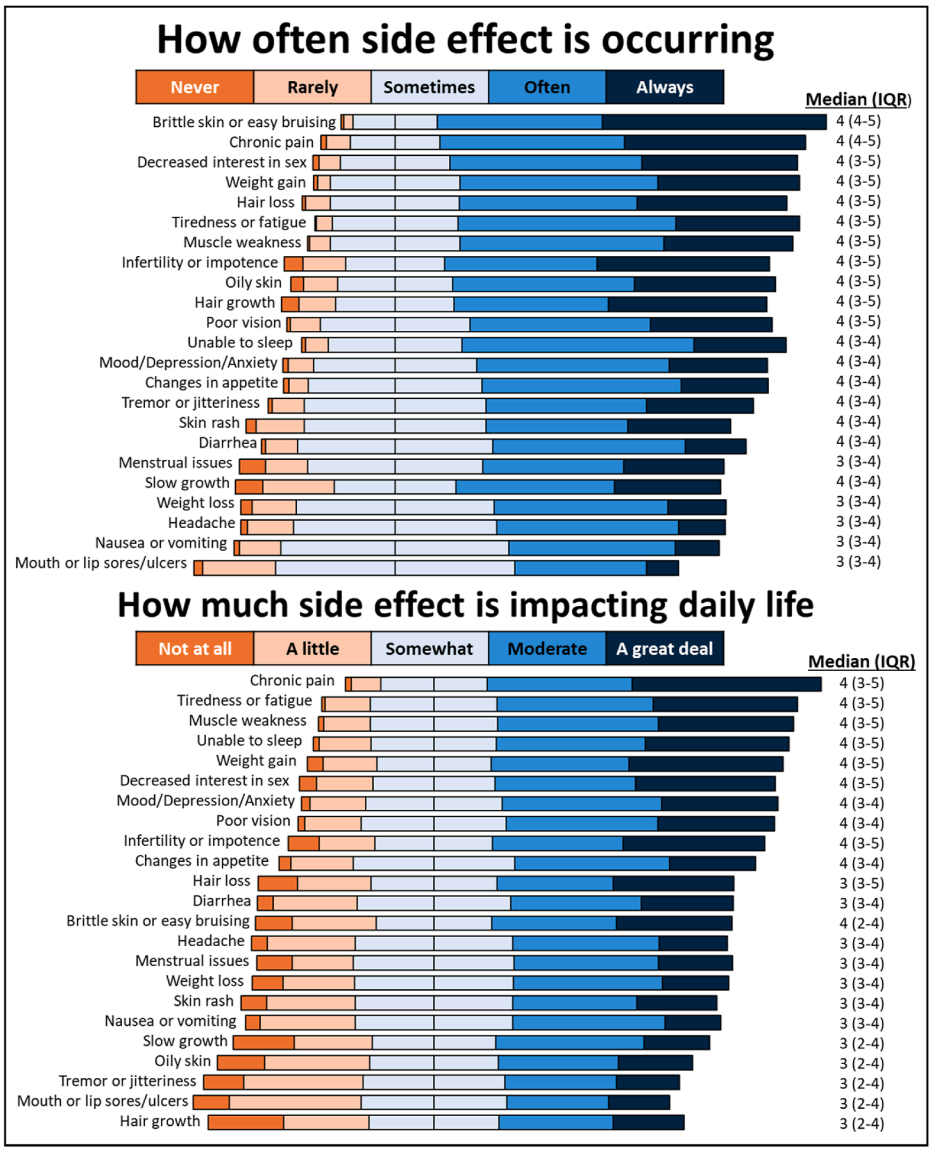

Figure 4. Side effect occurrence rate (top panel) and impact on daily life (bottom panel), ordered from most frequent/impactful to least common/impactful based on a 5-point Likert scale. IQR, interquartile range.

3.5. Medication adherence, costs, confidence, self-efficacy, and trust

Medication adherence was, in general, reported as "high" to "very high" by most respondents (Supplementary Table 9). More than 75% of respondents reported that they "agreed" or "strongly agreed" with knowing how to take their medications, why they are taking them, and believe the medications are working. More than 75% also reported they "almost always" or "always" take medications as recommended and remember to take doses. However, more than 1 in 4 reported "rarely" or "sometimes" not taking medications due to side effects. Medication costs were a significant issue reported by survey respondents (Supplementary Table 10). Nearly 40% of respondents missed a fill or refill in the past year due to costs, and more than 1 in 4 reported they skipped or reduced doses due to costs either "sometimes" or "often."

Confidence in understanding and adhering to medication regimens was reported as strong, with most respondents reporting being quite or very confident in taking several different medication schedules, remembering to take medications, listing medications and doses, actively participating in treatment plans, and knowing what to do when forgetting to take medications (Supplementary Table 11). Following doctors' directions and actively participating in treatment decisions was rated with the highest confidence. Health literacy was also rated high, with more than two-thirds of respondents being quite or extremely confident in filling out medical forms by themselves and using electronic devices to manage medications (Supplementary Table 12). Finally, trust in transplant providers and the team was also rated high (Supplementary Table 13). Nearly 75% of respondents "agreed" or "strongly agreed" that the transplant team puts their needs first, that they trust the team and always follow their advice, trust their judgment regarding medical care,

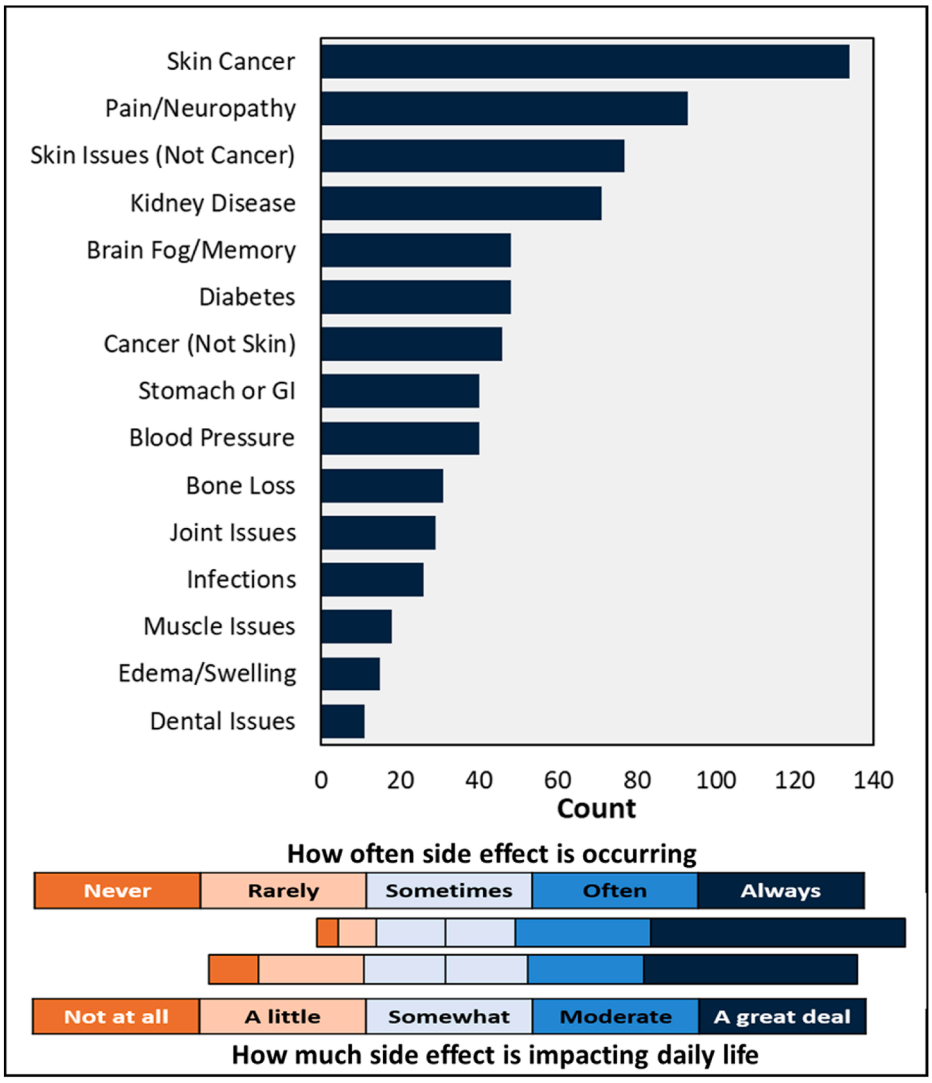

Figure 5. List of the most common write-in side effects with counts (top) and impact on daily life (bottom) based on a 5-point Likert scale. The total number of write-in side effects was 1135.

believe the team has experts, makes decisions that are best for them, and they have overall complete trust in the team. Two areas that were rated slightly lower than others regarding trust were feeling like a second opinion is needed and doing whatever the team tells them to do.

3.6. Language and discrimination

A small minority (6%) of respondents reported barriers with conversing or reading in English (Supplementary Table 14). On average, patients in the survey reported conversing and reading in English either "well" or "very well." Approximately 20% of respondents reported at least 1 experience with discrimination (Supplementary Table 15). Most commonly, this involved receiving less courtesy than other people, people thinking they were not smart, or people acting as if they were afraid of them. Of those reporting discrimination, most reported it as occurring either a few times per month, once weekly, or almost every day (Supplementary Table 16). Common reasons for discrimination included physical appearance, race, gender, age, or weight (Supplementary Table 17).

4. Discussion

This is the largest and most comprehensive survey of organ transplant recipients' perceptions of immunosuppression use and treatment experiences ever undertaken.[14,16-19] The study provides an intricate and mixed picture regarding perceived success and unmet needs from organ transplant recipients. On one hand, transplant recipients and pediatric caregivers completing this survey reported that trust in providers is incredibly important, and most have high or extremely high trust in the transplant team and their medical decision-making capacity. Patient-reported adherence, self-efficacy, engagement, and confidence were also high. HRQoL, treatment experience, and self-management were rated, in general, as fair to good. On the other hand, medication side effects, costs, and treatment burden were substantial issues with clear unmet patient needs.

Table 2
Baseline characteristics and immunosuppressants significantly associated with side effect burden.

Model variable	Relative impact on side effect burden (95% CI)	*P* value
Sociodemographics		
Unemployed due to disability	29% (27%-31%)	<.001
Multirace	25% (21%-30%)	.001
Age >60 y	23% (22%-24%)	<.001
College education	22% (21%-23%)	<.001
Transplant <10 years ago	22% (20%-23%)	<.001
White race	22% (20%-23%)	<.001
High school education	21% (19%-22%)	.038
Female gender	14% (14%-15%)	<.001
Current immunosuppression		
Tacrolimus	26% (24%-27%)	<.001
Mycophenolic acid	22% (21%-23%)	<.001
Prednisone	22% (21%-23%)	<.001
Mycophenolate mofetil	21% (20%-23%)	<.001
Past immunosuppression		
Other therapy	23% (20%-27%)	.003
Tacrolimus	23% (22%-25%)	<.001
Everolimus	22% (20%-24%)	.004
Prednisone	21% (20%-23%)	.001
Mycophenolate mofetil	21% (20%-22%)	.003
Sirolimus	20% (19%-22%)	.045

CI, confidence interval.

Side effects were nearly universally reported, occurred at a high frequency, and caused significant burdens in their daily lives. Infections and cancers were rated as more concerning compared to loss of graft function and rejection. Kidney disease, brain fog, hypertension, and diabetes were well recognized by respondents as common and debilitating side effects of immunosuppression. Importantly, 1 in 4 patients reported skipping or missing doses due to side effects, and almost half had skipped fills or refills of medications due to costs. The somewhat contradictory findings of high side effect frequency/burden, yet only 1 in 4 reporting skipping/missing doses, may reflect an element of social desirability bias among respondents, even though the survey was anonymous. Notwithstanding the large sample size and representatives of the survey, respondents were an average of 6 years posttransplant and therefore represent a surviving population with considerable lived experience and success negotiating the complexities of posttransplant care.[20,21]

This study provides contemporary evidence on top of the large body of literature that has assessed side effects and symptoms experienced by transplant recipients over the past several decades.[4,14] Although transplantation extends and improves the quality of life, immunosuppression induces a significant burden on recipients' lives. The consequences of immunosuppression, most notably chronic kidney disease, infections, cancers, diabetes, and hypertension, are well-known to transplant patients who report substantial hardships from these consequences. Despite this burden, there were relatively low levels of heterogeneity in immunosuppression regimens, and 25% of respondents reported no change in their regimen since transplant. This homogeneity may be due to relatively few medication options and/or to the few novel therapies approved to prevent rejection in nearly 15 years.[10] However, the most recent agent, belatacept, available since 2011, is rarely used despite having a significantly improved side effect profile.[9] Clearly, the focus on short-term outcomes and minimizing acute rejection still appears to be the predominant provider motivation of therapeutic decision making, even in patients who are years post-transplant and experiencing significant toxicities to current regimens. Low utilization of belatacept can also be interpreted as practitioners wanting to limit the risk of early rejection in lieu of long-term improved function.[12,13]

Our findings support the ongoing call for a paradigm shift in transplantation—one that places comparable emphasis on patient-reported outcomes, including treatment burden and HRQoL, with preventing acute rejection.[11] Adding key safety and tolerability endpoints to the systematic assessment of the risk-benefit of new immunosuppressants would help address this issue.[12,13] Further, focusing on the incidence and severity of known immunosuppression complications, including infections, cancers, kidney disease, diabetes, tremor, insomnia, brain fog, and hypertension, as important differentiating properties when comparing regimens in clinical trials can provide transplant clinicians with more options when encountering recipients with these issues. Although using 1-year efficacy failure (acute rejection, graft loss, death, and loss to follow-up) as an endpoint makes clinical trials feasible to develop and conduct, they inevitably lead to noninferiority studies—ones that do not provide enough insight into which agents may offer benefits beyond these important, yet short-term measures.[11-13] Noninferiority studies do not provide enough insight into the potential advantages and disadvantages of current versus novel regimens. Further, given our current regulatory environment, transplant clinicians may be less likely to test new agents about which they know little. Yet history shows us, through the low utilization of belatacept, that more needs to be done to make this a point of emphasis in the clinic when recipients display significant toxicities or side effect burdens, and clinical decision-making is occurring. Therapeutic inertia is a real problem in transplantation, and the causes and consequences of this deserve more research to address this issue, especially as the age of adult transplant recipients' increases. Older adult recipients have a reduced risk of rejection but an increased risk of adverse

events; yet they typically receive the same immunosuppressive regimen as much younger recipients.[19,22,23] It is recommended that transplant trials that include noninferiority endpoints, such as efficacy failure, also include testing for superiority of outcomes important to patients and clinicians (eg, organ function, safety, tolerability, and/or patient-reported outcomes as coprimary and/or key secondary endpoints).

Our survey results also provide insights into areas of success and promise for the future of transplantation. HRQoL was rated as good to very good for most patients.[24,25] Patients reported not feeling that the intense monitoring and follow-up required after transplant causes a lot of hardship, although it does interfere with work and leisure travel, hobbies, and other activities. Finally, the transplant population responding to this survey, in general, appeared to be highly engaged in self-care, self--efficacy, and adherence to regimens. These findings are encouraging because they suggest that as the transplant professional community works to address the burdens of current immunosuppression regimens, our patients will continue to work with us to develop and study new interventions. However, these responses should be considered in the context that nonadherence is an important factor in premature graft failure and that therapies that make it easier for patients to consistently achieve therapeutic levels of drug exposure are urgently needed. Respondents also reported concerns about medication costs and experiences of discrimination.[26-28] Both issues are complicated and multifactorial. The transplant community must continue to address health care–related costs through advocacy and public policy.[29] Despite passage of the Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act, cost considerations continue to compromise access to life-saving immunosuppressive drugs and remain a critical challenge for transplant recipients. Discrimination needs to be addressed at a larger societal level, but the transplant community can continue to address disparities and biases in communications, clinical care, and clinical policies.[29]

There are several limitations to this study. First, there was no way to ensure that respondents were transplant recipients. We implemented a detailed and thorough validation system, and the findings regarding the demographic characteristics and immunosuppression regimens are consistent with national registry data.[15] Further, because the web-based survey is only available in English or Spanish, patients without internet access and/or those who do not use smartphones, computers, or tablets, including socioeconomically disadvantaged patients, rural and remote dwellers, or patients with limited language proficiency in English or Spanish, may be underrepresented. Third, because dissemination was through transplant centers and the internet, patients who were not actively followed by a transplant center or engaged with a transplant organization may be underrepresented. However, the baseline characteristics demonstrate that our very large sample is representative of transplant recipients in the US and that our findings are broadly generalizable to the current US organ transplant population but may not be applicable to other international transplant populations or certain minoritized groups and may be prone to volunteer bias. The survey was overrepresented by non-Hispanic White participants (71%), as compared to SRTR data. However, the survey included substantial numbers of Hispanic and non-Hispanic Black participants. Asian participants and other racial/ethnic groups represented relatively small numbers, and these findings may not be fully applicable to these populations. Regarding medication side effects, it is important to note that in some cases, the cause of certain symptoms (eg, fatigue) may be difficult to attribute to disease or medication. In other cases, even when a symptom could theoretically be due to either of these causes, the timing of its occurrence in relation to when medications were started and stopped can help identify the cause with a good degree of certainty. These factors should be considered in the interpretation of patient-reported side effects when attribution is a concern.

In summary, the findings from this large-scale comprehensive survey of solid organ transplant recipients' treatment experience demonstrate a high level of confidence in health care providers and engagement in self-care, but also substantial treatment burden related to immunosuppression side effects and concerns about long-term medication safety. The insights regarding the universally experienced day-to-day challenges of having to take lifelong immunosuppression reveal large unmet therapeutic needs that have been, to date, overshadowed by the enduring need to minimize acute rejection. These findings suggest that premature graft failure is related to the shortcomings of current immunosuppressive therapies and provide a strong rationale to drive reforms on how the safety and efficacy of transplant therapies are measured, compared, and approved by regulatory authorities in clinical trials.

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Declaration of competing interest

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Data availability

Data availability The data that support the findings of this study are available on request from the corresponding author after regulatory review and approval.

Appendix A Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2025.07.2474.

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