Donor Lung Sequence Number and Survival after Lung Transplantation in the United States

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Online Supplemental Materials

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EMethods

This study was approved by the University of Pennsylvania Institutional Review Board.

Data sources

This study used data attained from the United States (U.S.) Organ Procurement and Transplantation Network (OPTN) provided by the United Network for Organ Sharing (UNOS). Specifically, we used the Potential Transplant Recipient (PTR) database which included information on the match-run outcomes for all donor lungs that resulted in a transplant and the UNOS Standard Transplant Analysis and Research (STAR) file. The STAR file contains information on all waiting list registrations and transplants performed in the U.S. since October 1, 1987.

In this section, we summarize selected information provided with the PTR dataset relevant to the evaluation of this study. The PTR dataset provided data generated and recorded during the organ allocation process since April 2007. Data elements included a ranked listing of candidates created when a match was run for a specific organ, with a list up to and including the final acceptor. For each offer, there is an indicator if that organ offer was accepted for the individual patient, and if not, the reason for refusal provided by the lung transplant center. The PTR database has limitations, however. For example, organs that were offered, but not accepted by any U.S. program are not included in the database. Further, it is possible for an organ to be accepted for transplant, but not ultimately transplanted due to emergent issues with either the recipient or donor/organ.

There are three ways in which a refusal reason can be provided: primary reason, secondary reason, or using free-text. For this study, we only examined pre-established, numerically submitted, primary reasons for refusal (see list below).

In certain situations, a candidate/center ranked on the match-run was marked as a "bypass" to indicate that the candidate/center never actually received an offer. Reasons for bypass may include, but are not limited to, directed donation, donor medical urgency that required expedited acceptance, natural disasters, or factors associated with waiting time. A bypass does not change the documented sequence number, as the ranking remains as it was initially generated. Thus, we report the sequence number as observed, but recognize that in some instances the sequence number may suggest an artificially high number of preceding organ offers due to bypasses. We made this decision with the logic that the reported sequence number was the actual number seen by transplant centers.

Exclusion criteria

To prepare our analytic sample we applied restrictions that would conceivably result in different decision-making or organ suitability assessment. First, we removed offers to patients who were < 18 years of age at listing (i.e., pediatric offers). Second, we removed offers to patients listed for multi-organ transplant as a decision to accept an offer may be related to factors external to the lung offer, such as the quality or availability of another organ. Finally, we

removed offers to patients who had any prior transplant as the suitability of an offer may be differentially selective for these individuals.

Categorization of lung offer refusal codes

We summarized and, in certain instances, collapsed primary refusal codes provided in the PTR database as follows:

1) Donor age or quality: (#830),
2) Donor size/weight: (#831),
3) Organ-specific donor issue: (#837),
4) Multiple organ transplant or different laterality is required: (#802),
5) Donor infectious concerns:
   a. #833 = donor social history; and,
   b. #834 = positive serological tests.
6) Operational/logistical/recipient issues:
   a. #800 = candidate's condition improved, transplant not needed;
   b. #801 = recipient ill, unavailable, refused, or temporarily unsuitable;
   c. #803 = candidate transplanted (pending offers);
   d. #820 = heavy workload;
   e. #822 = exceeded 1-hour response time;
   f. #823 = surgeon unavailable;
   g. #824 = distance to travel or ship;
   h. #825 = operational – transplant center;
   i. #832 = donor ABO;
   j. #835 = organ preservation;
   k. #836 = organ anatomical damage or defect; and,
   l. #860 = medical urgency of another candidate.
7) Human leukocyte antigen (HLA) issue:
   a. #810 = positive crossmatch;
   b. #811 = number of HLA mismatches unacceptable;
   c. #812 = no serum;
   d. #813 = unacceptable antigens;
   e. #814 = high PRA; and,
   f. #815 = high CPRA.
8) Refusal code listed as other: (#898).

Analysis and considerations regarding lung offers that were bypassed

Bypasses can occur for numerous reasons such as medical urgency or directed donation. Prior to applying recipient exclusion criteria, we removed donor match-runs associated with a direct donation (n = 10) and where the maximum offer limit was exceeded (n = 2). We then evaluated each individual match-run that had a bypass including the free-text explanation for a bypass when provided. The goal of this assessment was to (i) have a clear rationale for excluding any match-runs from the sample while (ii) seeking to include match-runs

with meaningful sequence numbers in our analysis. In this process, we identified three patterns that guided the construction of our primary analytic sample. Overall, the first observed bypass in a match-run tended to occur after several lung offer refusals had accrued. Thus, while a bypass may have inflated the final sequence number, it was rarely the initial driver to a higher sequence number. Relatedly, bypasses were comparatively rare and isolated. For example, of the 11,547 potentially eligible match-runs before merging the PTR and UNOS dataset, 1,154 (9.9%) had at least 1 bypass; 305 (2.64%) had only one bypass, 144 (1.25%) had two bypasses and 4.74% had ≥ 5 bypasses. Further, nearly 60% of the match-runs with a bypass did so for a free-text explanation, and we found that the majority of free-text entries aligned with existing lung offer refusal codes shown above (e.g., lack of serum, need for bilateral transplantation, or transplant center operational factors). Finally, we observed that lung transplant center refusals still occurred after the first bypass occurred in a match-run. Thus, based on clinical experience and the observation that over 50% of lung offers were accepted by the 5th lung offer, we chose to remove donor match-runs that had their first bypass occur in the first 5 offers (sequence numbers 1 to 5) for emergent reasons, multi-organ placement, or an irreconcilable free-text field. Though any cut point has inherent arbitrariness, we felt that this approach included match-runs that resulted in higher sequence numbers due to lung offer refusals by at least the 5 highest ranked lung transplant candidates. That is, after careful assessment of the reasons for bypasses we acknowledge that the sequence number at acceptance may be inflated for a small percentage of the sample, but in all cases where a bypass occurs in our data, the sequence number truly reflects prior lung offer refusals.

Empirical analysis

Description of refusal reasons for lung offers

We separated the presentation of the lung offer process by what we termed as the initial and secondary sequence. Specifically, for lung offers that resulted in a single lung transplant, the other lung would then continue to be offered as a single lung only, and thus alter refusal reasons for subsequent transplant. Therefore, we present the results from the initial and secondary sequence separately.

Factors associated with later acceptance in the match-run

We used two modeling approaches for this part of our analysis. In addition, we examined several different contrasts as there was no obvious sequence number cut point. First, we estimated multinomial logistic regression models where we categorized sequence numbers at acceptance into four categories: 1 and 2, 3 to 10, 11 to 50 and ≥ 51. We present two models, one with sequence numbers 1 and 2 as the reference category and the other using 3 to 10 as the reference category. Next, we estimated logistic regression models comparing groups of sequence numbers as follows:
1) Acceptance at sequence number 1 versus sequence numbers 2 to 10,
2) Acceptance at sequence numbers 1 to 5 versus sequence numbers 6 to 10,
3) Acceptance at sequence numbers 1 to 10 versus sequence numbers ≥ 11,

4) Acceptance at sequence numbers 1 to 25 versus sequence numbers ≥ 26,
5) Acceptance at sequence numbers 1 to 50 versus sequence numbers ≥ 51, and
6) Acceptance at sequence numbers 1 to 99 versus sequence numbers ≥ 100.

The models shown in figures E2 and E3 took into account dependence among observations that involved the same donor using a robust sandwich variance estimator (1). We could not estimate mixed-effects multinomial logistic regression models with a transplant center random intercept but observed similar results when using a robust sandwich variance estimator for transplant center instead of donor. Mixed-effects logistic regression models with a transplant center random intercept also showed similar results, however, the effect sizes were generally attenuated (Figure E4).

We did not seek to build a causative or predictive model for this analysis. Rather, we sought to assess adjusted associations with later organ acceptance based on several different sequence number thresholds using a small set of hypothesized mechanisms as our modeling strategy.

EReferences

1. Wooldridge JM. Econometric analysis of cross section and panel data: 2nd Edition. Cambridge, Massachusetts: MIT Press; 2010.

Table E1. Summary of variables used in the multivariable regression models of acceptance. SN = sequence number at the time of acceptance; CNS = central nervous system; pO2 = partial pressure of oxygen.

		Overall n = 10,981	SN 1 & 2 n = 4,091	SN 3 to 10 n = 3,550	SN 11 to 50 n = 2,464	SN ≥ 51 n = 876
Annual center volume	Low	6035 (55.0%)	2823 (69.0%)	1882 (53.0%)	1058 (42.9%)	272 (31.1%)
	Medium	2309 (21.0%)	804 (19.7%)	917 (25.8%)	497 (20.2%)	91 (10.4%)
	High	2637 (24.0%)	464 (11.3%)	751 (21.2%)	909 (36.9%)	513 (58.6%)
Day of offer	Weekday	6433 (58.6%)	2463 (60.2%)	2076 (58.5%)	1420 (57.6%)	474 (54.1%)
	Weekend	4548 (41.4%)	1628 (39.8%)	1474 (41.5%)	1044 (42.4%)	402 (45.9%)
Bronchoscopy results	Normal	7976 (72.6%)	3064 (74.9%)	2619 (73.8%)	1715 (69.6%)	578 (66.0%)
	Abnormal	2417 (22.0%)	818 (20.0%)	751 (21.2%)	607 (24.6%)	241 (27.5%)
	Missing	588 (5.4%)	209 (5.1%)	180 (5.1%)	142 (5.8%)	57 (6.5%)
Public Health Service increased-risk donor	No	9959 (90.7%)	3749 (91.6%)	3252 (91.6%)	2204 (89.4%)	754 (86.1%)
	Yes	1004 (9.1%)	335 (8.2%)	291 (8.2%)	258 (10.5%)	120 (13.7%)
	Missing	18 (0.2%)	7 (0.2%)	7 (0.2%)	2 (0.1%)	2 (0.2%)
Donor smoking history	No	9794 (89.2%)	3730 (91.2%)	3185 (89.7%)	2154 (87.4%)	725 (82.8%)
	Yes	1071 (9.8%)	323 (7.9%)	330 (9.3%)	284 (11.5%)	134 (15.3%)
	Missing	116 (1.1%)	38 (0.9%)	35 (1.0%)	26 (1.1%)	17 (1.9%)
Pulmonary infection	No	5309 (48.3%)	2053 (50.2%)	1707 (48.1%)	1154 (46.8%)	395 (45.1%)
	Yes	5672 (51.7%)	2038 (49.8%)	1843 (51.9%)	1310 (53.2%)	481 (54.9%)
Donor cause of death	Trauma	5026 (45.8%)	1898 (46.4%)	1726 (48.6%)	1057 (42.9%)	345 (39.4%)
	Anoxia	1687 (15.4%)	571 (14.0%)	518 (14.6%)	419 (17.0%)	179 (20.4%)
	CNS tumor	77 (0.7%)	26 (0.6%)	26 (0.7%)	18 (0.7%)	7 (0.8%)
	Stroke	3910 (35.6%)	1489 (36.4%)	1203 (33.9%)	906 (36.8%)	312 (35.6%)
	Other	281 (2.6%)	107 (2.6%)	77 (2.2%)	64 (2.6%)	33 (3.8%)
Chest radiograph results	Normal	6058 (55.2%)	2304 (56.3%)	2035 (57.3%)	1323 (53.7%)	396 (45.2%)
	Abnormal	4850 (44.2%)	1765 (43.1%)	1483 (41.8%)	1130 (45.9%)	472 (53.9%)
	Missing	73 (0.7%)	22 (0.5%)	32 (0.9%)	11 (0.4%)	8 (0.9%)
pO_2	Normal	7874 (71.7%)	2896 (70.8%)	2557 (72.0%)	1765 (71.6%)	656 (74.9%)
	Low	3037 (27.7%)	1161 (28.4%)	976 (27.5%)	683 (27.7%)	217 (24.8%)
	Missing	70 (0.6%)	34 (0.8%)	17 (0.5%)	16 (0.6%)	3 (0.3%)

Figure E1. Percent of lung offers accepted at (Panel A) each sequence number and then separated by (Panel B1) first lung offer sequence and (Panel B2) second lung offer sequence. Offer acceptances at sequence number 100 (n = 2) or above a sequence number of 100 (n = 371) were combined so that all offers could be visualized.
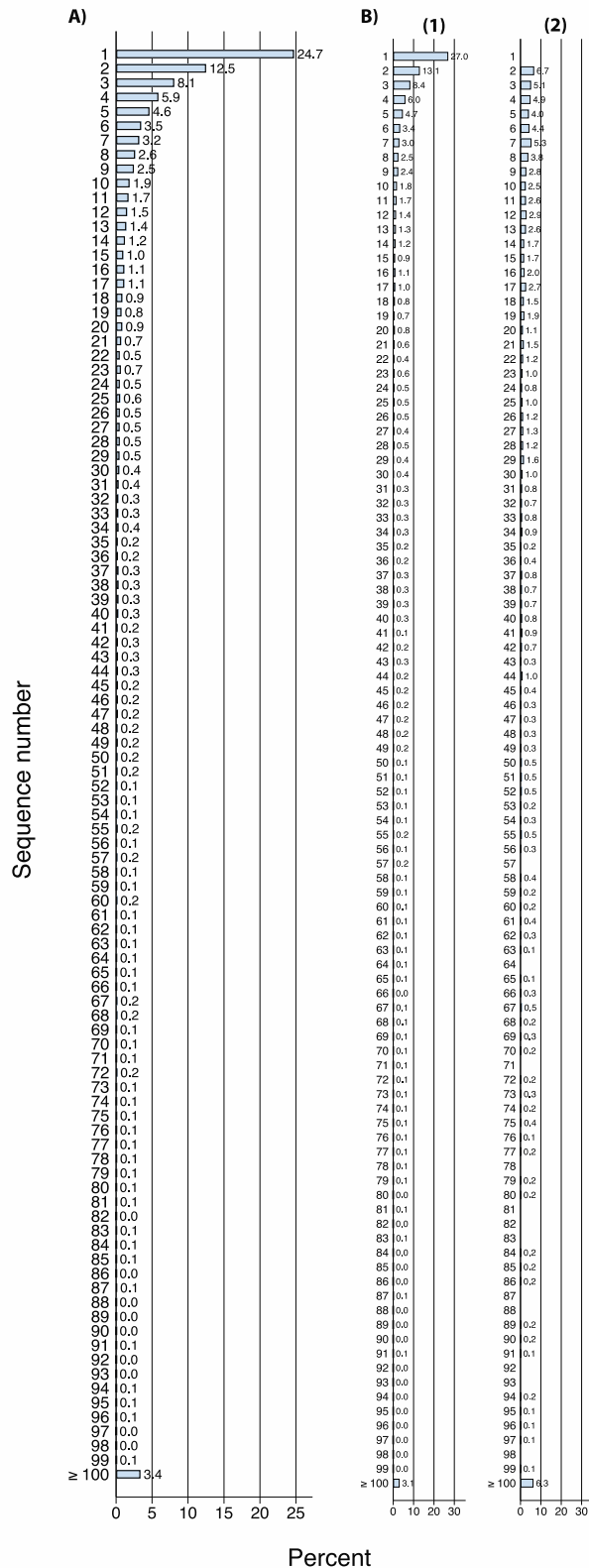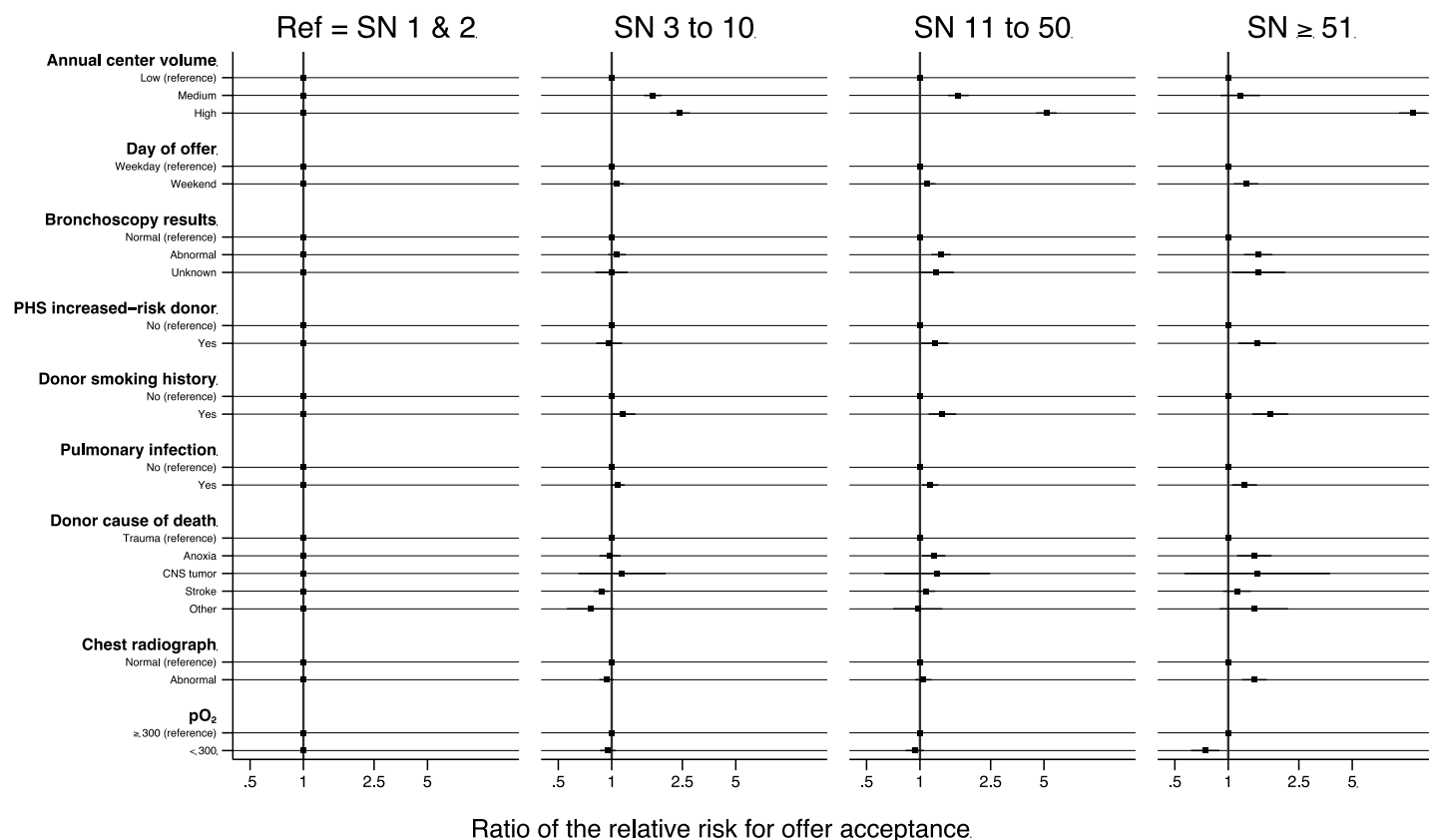
Figure E2. Multinomial logistic regression models comparing categories of sequence numbers (SNs) at the time of offer acceptance. Each panel has one reference category and three comparisons. Panel A compares SN acceptances at offer 1 or 2 to SNs 3 to 10, 11 to 50, and $\geq$ 51. Thus, all coefficients are equal to 1 for SN acceptances 1 or 2 in Panel A. In Panel B the reference category is SN acceptances 3 to 10. The coefficients and 95% confidence intervals from multinomial logistic regression models indicate the ratio of relative risks, not odds ratios. The following "missing" categories were included in the model, but not shown due to their small sample sizes (Public Health System [PHS] increased-risk donor, donor smoking history, partial pressure of oxygen [pO_2], and chest radiograph, see Table E2). Each model was adjusted for clustering at the donor level. CNS = central nervous system.

A) **Reference category is sequence numbers 1 and 2**

Ratio of the relative risk for offer acceptance

B) Reference category is sequence numbers 3 to 10
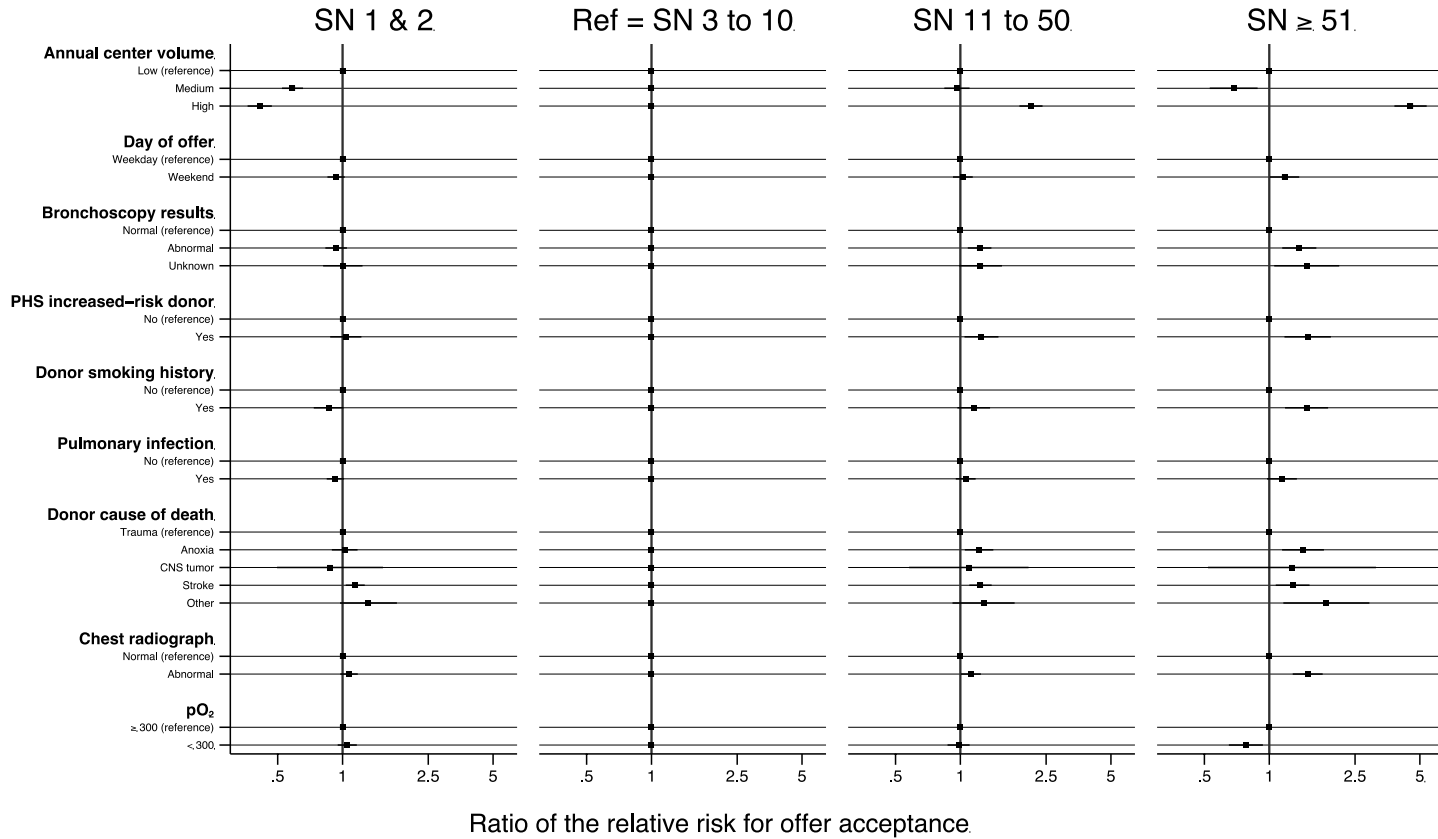

Ratio of the relative risk for offer acceptance

Figure E3. Six separate logistic regression models comparing different categories of sequence numbers (SNs) at the time of offer acceptance. The first two models (left to right) were restricted to offers accepted by or on offer 10. The remaining four models compared categories based on the entire analytic sample. The following "missing" categories were included in the regression analysis so that no offers or individuals were excluded, however, they were not shown due to their small sample sizes (Public Health System [PHS] increased-risk donor, donor smoking history, partial pressure of oxygen [pO$_2$], and chest radiograph, see Table E2). Each model was adjusted for clustering at the donor level. CNS = central nervous system.
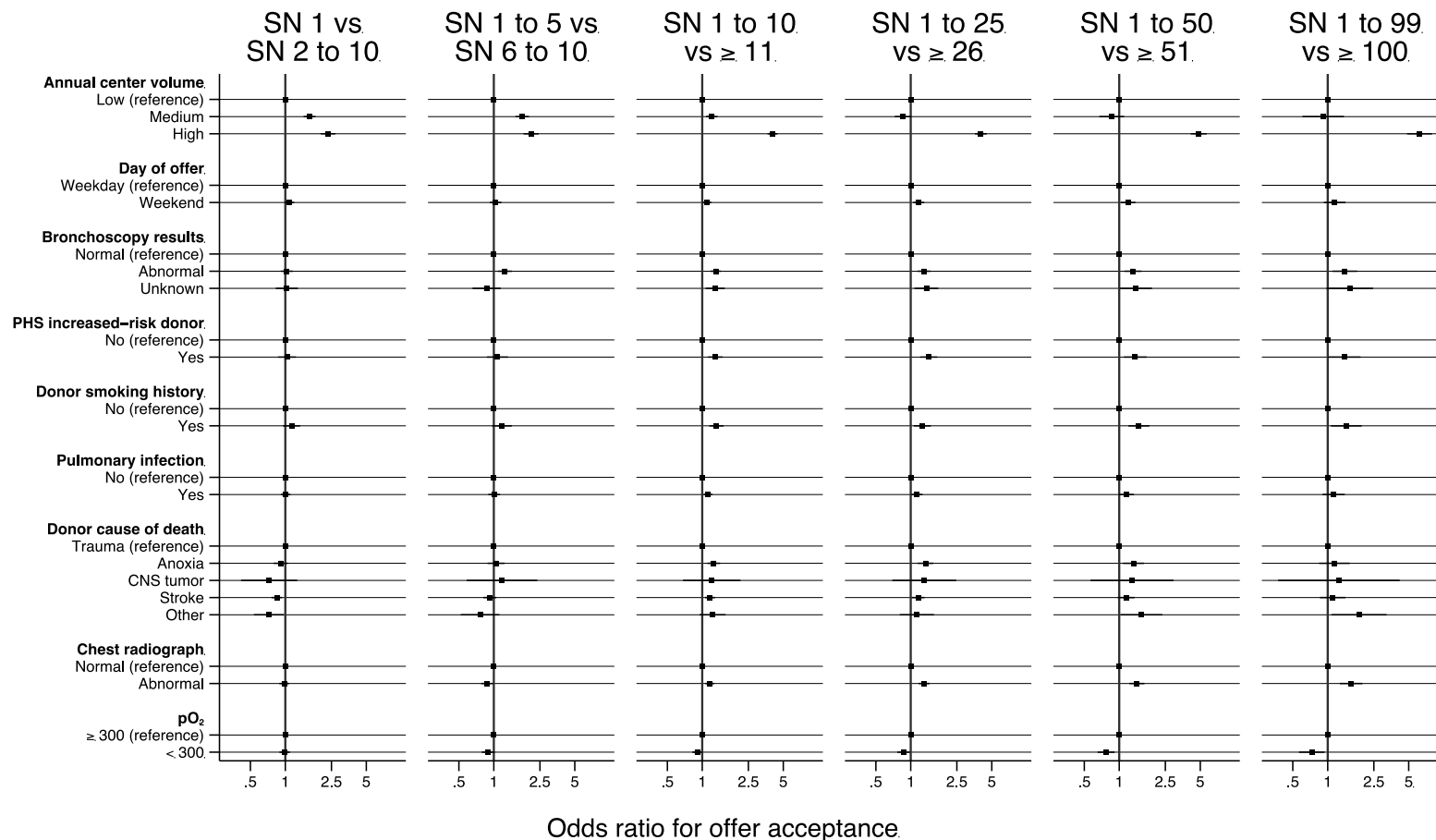
Figure E4. Six separate mixed-effects logistic regression models comparing different categories of sequence numbers (SNs) at the time of offer acceptance. The first two models (left to right) were restricted to offers accepted by or on offer 10. The remaining four models compared categories based on the entire analytic sample. The following "missing" categories were included in the regression analysis so that no offers or individuals were excluded, however, they were not shown due to their small sample sizes (Public Health System [PHS] increased-risk donor, donor smoking history, partial pressure of oxygen [pO$_2$], and chest radiograph, see Table E2). Each model included a transplant center random intercept. CNS = central nervous system.

Odds ratio for offer acceptance