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Surgical quality in organ procurement during day and night; an analysis of quality forms

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Surgical quality in organ procurement during day and night; an analysis of quality forms

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Author contributions:

J.D. de Boer, K.E.A. van der Bogt and A.E. Braat hypothesized that a relationship may be present between time of day and the incidence of surgical injury. Dr. Van der Bogt is involved in the Fit to Perform trial currently performed in The Netherlands. Data on procured organs are provided by all six transplanting centers in the Netherlands to the Dutch Transplant Foundation. Permission to use these was granted by delegates from all centers; R.A. Pol (Groningen), J. de Jonge (Rotterdam), C.H.C. Dejong (Maastricht), W.N. Nijboer (Leiden) and J.A. van der Vliet (Nijmegen). Data were then obtained via the Dutch Transplant Foundation where K. Ooms-De Vries and B. Haase were involved. Data were analysed and statistical analysis was performed and interpreted by J.D. de Boer, K.E.A. van der Bogt, A.E. Braat and H. Putter of the Statistical Department. The manuscript was then drafted by J.D. de Boer, K.E.A. van der Bogt, A.E. Braat and H. Putter. The draft manuscript was critically revised by all involved.

Abbreviations:

DCD, Donor after determination of circulatory death

DBD, Donor after determination of brain death

QF, Quality form

Data sharing agreement

Data are available upon request at the Dutch Transplant Foundation. Plesmanlaan 100, 2332 CB, Leiden.

Words: 2,284 words

Abstract (252 words)

Objectives

To analyse a potential association between surgical quality and time of day.

Design

A retrospective analysis of complete sets of quality forms filled out by the procuring and accepting surgeon on organs from deceased donors.

Setting

Procurement procedures in the Netherlands are organized per region. All procedures are performed by an independent, dedicated procurement team that is associated with an academic medical center in the region.

Participants

In 18 months' time, 771 organs were accepted and procured in The Netherlands. Of these, 17 organs were declined before transport and therefore excluded. For the remaining 754 organs, 591 (78%) sets of forms were completed (procurement and transplantation). Baseline characteristics were comparable in both groups with the exception of height (p=0.003).

Primary outcome measure

All complete sets of quality forms were retrospectively analyzed for the primary outcome, procurement related surgical injury. Organs were categorized based on the starting time of the procurement in either day- (8AM–5PM) or evening/night-time (5PM-8AM).

Results:

Out of 591 procured organs, 129 organs (22%) were procured during daytime and 462 organs (78%) during evening/night-time. The incidence of surgical injury was significantly lower during daytime; 22 organs (17%) were injured during daytime compared to 126 organs (27%) during evening/night-time procurement (p=0.016). This association persists when adjusted for confounders.

Conclusions:

This study shows an increased incidence of procurement related surgical injury in evening/night-time procedures as compared to daytime. Time of day might (in)directly influence surgical performance and should be considered a potential risk factor for injury in organ procurement procedures.

Strengths and limitations

- Quality of procurement is evaluated by two specialists; once by the procuring and once by the accepting surgeon. (+)
- All procedures are performed by a dedicated, certified procurement team. This ensures a high standard of procurement quality. (+)
- Selection bias in the timing of procurements is minimally present because the planning is mainly logistical rather than medical. (+)
- Injury is evaluated in a categorical way (yes/no) to analyze surgical performance in a broad sense. It avoids a loss of detailed information but limits a sub analysis on injuries leading to discarding organs.
- Conclusions may be limited by the number of procured organs. (-)

Introduction

Nights shifts have been shown to pose a higher risk for errors and self-injuries in several medical settings[1–4]. A negative effect of nights shifts might be caused by factors associated with fatigue and circadian rhythm[5] and could also affect surgical performance. The potential relation between timing of procedures and surgical performance, is however not clear. Studies have reported conflicting results[6–10] and timing of procedures might therefore affect patients' safety. The discussion on the topic, has contributed to reforms in working hours for surgical residents in the US, as well as in Europe.

The lack of evidence for a causative relationship between fatigue related factors and inferior performance in surgery is interesting considering the extensive amount of evidence in other fields[11,12]. Although it might hold true that surgical performance is not affected by fatigue or time of day, it could also be a consequence of an insufficiently sensitive measurement of technical proficiency. To measure surgical performance, a negative clinical outcome in patients would be the most obvious endpoint. This has however some limitations. A clinical endpoint might lead to a loss of detailed information because only severe intra-operative injuries are likely recognized for their clinical impact while minor injuries might be missed. Secondly, it is very difficult to relate a specific surgical action to an event in a patient. On one hand, because not all intra-operative injuries are noticed, on the other, because outcome after surgical procedures is highly multi-factorial and complex. A potential (minor) effect of time of day on surgical performance might therefore not be noticed when solely focussing on clinical outcome measures.

The Dutch digital feedback system on the quality of organ procurement offers an opportunity to analyse surgical performance in detail. We have previously analysed this dataset on procurement related surgical injuries and found a high incidence of non-critical injuries. We furthermore, did not find a significant difference between the non-critically injured and intact

organs for one year graft survival[13]. In this study, surgical injury is considered as a sensitive proxy of surgical performance. We hypothesize that a relation is present between surgical performance and time of day.

Methods

We obtained data from the Dutch Transplant Foundation on quality forms filled out from March 2012 until September 2013. It comprises two forms on each individual abdominal organ that is procured and accepted in The Netherlands. One form is filled out by the procuring surgeon after procurement and remarks are placed in the second form by the accepting surgeon. Detailed information is registered on packaging, perfusion (time/volume/fluid), anatomy and possible injury of vessels or organs. In case of a discrepancy between the procuring and accepting surgeons, remarks of the accepting surgeon were considered leading. Pancreata procured for islet-isolation and organs that were declined before transportation to the accepting center were excluded.

We accepted starting time of the cold perfusion of the aorta as starting time of the procedure. For donation after circulatory determination of death (DCD) this is almost at the same time, but for donation after determination of brain death (DBD) this usually is 1 – 2 hours after skin incision. All organs were categorized in two groups; daytime (when procured between 8AM and 5PM) or evening/night-time (when procured between 5PM and 8AM). The incidence of injury as binary outcome (yes/no) was compared between both groups using univariate logistic regression with time of day as sole covariate. The analyses were adjusted separately and for all available confounders related to procurement related injury in literature. These factors include body mass index (BMI) and donor type (DCD or DBD)[13]. Lastly, also height (cm) was included in the univariate and multivariate analysis since it was significantly different in both groups.

The relationship between injury and starting time of the procedure was visualized as a log odds ratio on a continuous 24 hours' scale by using splines regression. To correct for a possible correlation of injury within donor procedures, sandwich estimators of the standard

errors were used. A p-value of <0.05 was considered statistically significant and analyses were performed with SPSS version 22.0 and R version 2.3.3.

Patients were not involved in the development of the research question or in the design of the study. No ethical statement was required according to national ethical guidelines. Data are available upon request at the Dutch Transplant Foundation. Permission for this analysis was granted by the national competent authority, the Dutch Transplant Foundation, on April 6th, 2017.

Results

During the study period, 771 organs were accepted for transplantation. Out of these, 17 organs were declined during procurement and subsequently not transported and therefore excluded (5 livers, 8 pancreata and 4 kidneys). For all 754 accepted and transported organs, 591 forms were completed (591/754, 78%) on 133 livers (23%), 38 pancreata (6%) and 420 kidneys (71%). Response rates per organ were respectively 87%, 90% and 75%. There were 148 (148/591=25%) organs with reported injuries; 36 livers (36/133, 27%), 10 pancreata (10/38, 26%) and 102 kidneys (102/420, 24%). Of all injured organs, 12 (2%) were discarded because of this surgical injury; 1/133 (0.8%) liver, 5/38 (13%) pancreata and 6/420 (1.4%) kidneys ($p<0.001$).

Day and night-time operating hours

With the exception of donor height ($p=0.003$) organs were comparable in demographical characteristics in the daytime and evening/night-time groups in univariate analysis as shown in table 1.

Table 1. Demographics of the study population (n=591). Only height is different between the two groups (p=0.003).

	Daytime (8AM-5PM) n=129			Evening and nighttime (5PM-8AM), n=462			
	Mean (SD)	**Median**	**Range**	**Mean (SD)**	**Median**	**Range**	**p-value**
Age	51.8 (15.3)	55	14-76	52.2 (15.6)	55	10-78	0.772
Height	177.4 (7.1)	180	161-198	174.8 (9.4)	175	140-200	**0.003**
Weight	76.6 (13.4)	78	52-120	76.6 (15.1)	77	35-150	0.996
BMI	24.3 (3.6)	24.0	17.6-34.7	25.0 (4.1)	24.7	12.5-46.3	0.080
	n (%)			**n (%)**			
Sex							
Male	75 (58)			256 (55)			
Female	54 (42)			206 (45)			0.581
Donortype							
DBD	69 (53)			210 (45)			
DCD	60 (47)			252 (55)			0.106

Volume related regional effects that also may impact the risk of surgical injury[13], were not significantly different between both groups (data not shown). During daytime, 129 of 591 organs (22%) were procured and 462 organs (78%) were procured during evening/night-time. There was a significant lower chance of organ injury during daytime procurements; 22 organs (17%) were injured during daytime and 126 organs (27%) during evening/night-time (p=0.016).

Evening/night-time procedures remained a factor independent and significantly associated with injury (p=0.029) when univariate and multivariate adjusted for height, BMI and donor type.

Circadian points

Figure 1 shows an increased risk of injury for procedures that start in evening/night-time. The highest risk of organ injury was for procedures starting around 9PM, the lowest risk for procedures starting around 12PM (noon).

Discussion

This study shows a relationship between surgical performance and the starting time of the procurement procedure. A higher incidence of surgical injury is measured in evening/night-time procedures as compared to daytime procedures. This association persists when adjusted for important confounders.

The relation between surgical performance and timing of surgical procedures is often highly confounded. Patients have more complicated and/or acute problems during the night[14]. Also, access to imaging and laboratory testing as well as specialized OR nurses and anesthesiologists might be less available during night-time[13]. The study population of this study, abdominal organs from deceased donors, eliminates several of these confounders. Most procedures can generally be scheduled within 6-24 hours regardless of the cause of brain death because these patients are usually hemodynamically stable. A higher number of procurement procedures during evening/night-time therefore seems to rather reflect issues with operating room (OR) availability during the day than an abundance of emergency procedures. Secondly, abdominal organ procurement is well organized in The Netherlands; each sub region has a 24/7 availability of a self-supporting, certified organ procurement team. Such a team includes for daytime as well as for evening/night-time procedures two dedicated nurses as well as a dedicated anesthesiologist and two surgeons, of who at least one is certified for procurement procedures. They are not involved in other clinical activities while on duty. The extensive training to become certified and the absence of other clinical activities when on call, ensure a high quality of organ procurement and eliminates a major variance in operating staff. In addition, differences in hospital facilities (local vs. academical) should be minimal because the teams bring own standard supplies for the procedure. In our opinion, this offers a unique setting.

Another strength of this study are the very small differences in baseline characteristics of the day- and evening/night-time groups. Only donor height was different between both groups and so far this factor has not been described to influence the risk of organ injury. The similarity between both groups is likely associated with the planning of procedures; independent of donor characteristics and solely dependent of OR availability. Other relevant and non-measured donor associated variables like vascular anatomy can therefore be assumed to be equal in both groups since they do not affect the starting time of procedures. Factors that might have been different and might have influenced our results, include volume related regional effects as previously described[13]. The ratio between regions for day- and evening/night-time procedures was however not different (data not shown).

In this study, we evaluated all surgical injury in a strict categorical way (yes/no) to analyze surgical performance in a broad sense and to avoid a loss of detailed information. In further studies, it could be of relevance to further specify the definition, type and impact of injury. In the current data for example, the number of critical injuries –leading to discarding of the organ- (n=12) are insufficient for an adequate comparison in day- and evening/night-time groups.

A limitation of this study is the response rate for complete sets of forms of 80%; a higher response rate might have led to a higher reported number of (critical) injuries. Although the response rate could have been better, it is to be noted, that the current response rate concerns organs on which two forms are digitally filled out by two independent surgeons. This two-way registration can be considered to be precise and objective.

Our results are in accordance with (non-surgical) medical studies that report a negative relation between evening/night-time or fatigue related factors and performance; a higher rate of self-injuries among residents[3] and a decreased proficiency in surgical simulations after

night shifts[8]. These results are conflicting with large surgical database studies that show no difference in conversion rates during cholecystectomy or outcome in patients like the occurrence of serious adverse events[6,15]. Rothschild *et al.* on the other hand, found an increased rate of complications among post night-time surgical procedures performed by physicians with sleep opportunities of less than 6 hours[10]. A study on liver transplantations, found that operations during night-time took longer and were associated with a higher risk of early death, although without any effect on peri-operative complications or long-term survival[16]. Also in kidney transplantation, more peri-operative complications[17] but also less technical graft failure[18] were seen in night-time procedures. The latter did not take into account a difference in surgical experience between day- and night-time procedures; night-time procedures are rather performed by consulting surgeons as compared to daytime procedures that are usually performed by (supervised) surgical residents. In the current study however, all procedures are performed by the same group of dedicated surgeons and teams. These studies seem to report contradictory findings between short term or non-patient outcomes on the one hand and long-term outcome in patients. This observation, is reflected in our data; we notice a higher incidence of surgical injuries during night-time (this study) but no difference in one year graft survival between injured and intact organs in a previous analysis of the same cohort[13]. It indicates that the pathway leading to a negative outcome in surgical patients is complex and multi-factorial; only most severe surgical injuries might result in clinically measurable negative outcome. To find a significant difference in outcome in patients that can be related to the timing of procedures or 'fitness' of surgeons, higher numbers are probably needed. This study can therefore only assess (technical) surgical performance.

The increased injury rates during evening/night-time operating hours may indicate that surgical performance is affected by time of day. The etiology of this association is however

not yet clear. The negative effect of evening/night-time procedures suggests an effect of fatigue related factors. Fatigue was however not measured in this study and should theoretically play a smaller role because procurement teams can rest between procedures and do not participate in other clinical activities when on call. Other mechanisms might however contribute; the surgical injury pattern in this study shows, for example, a remarkable resemblance with circadian rhythm and associated biological hormone levels as observed in chronobiology[19]. To further identify the mechanism behind the higher injury rate during evening/night-time, it will be essential to objectively measure the surgeon's fitness before and after procurement. Current research on the validation and clinical application of such a "Fit to Perform" test is ongoing[20]. It might give an objective tool to evaluate the relation between the fitness of a surgeon and his surgical performance.

We believe this study shows, that evening/night-time procedures might present a suboptimal setting for organ procurement. Although the causal pathway is not yet clear, our results do suggest that time of day should be taken into account to optimize the quality of organ procurement. It may even be of relevance for other surgical procedures. This would mean that, in the absence of acute pathology, surgeries should be preferably performed during daytime.

Conclusion

This study shows an increased incidence of surgical injury in organ procurement procedures during evening/night-time, as compared to daytime. Time of day might (in)directly influence surgical performance and should be considered a potential risk factor for injury in organ procurements.

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Figure legends:

Figure 1. The relationship between starting time of the cold perfusion of the aorta and risk of injury.

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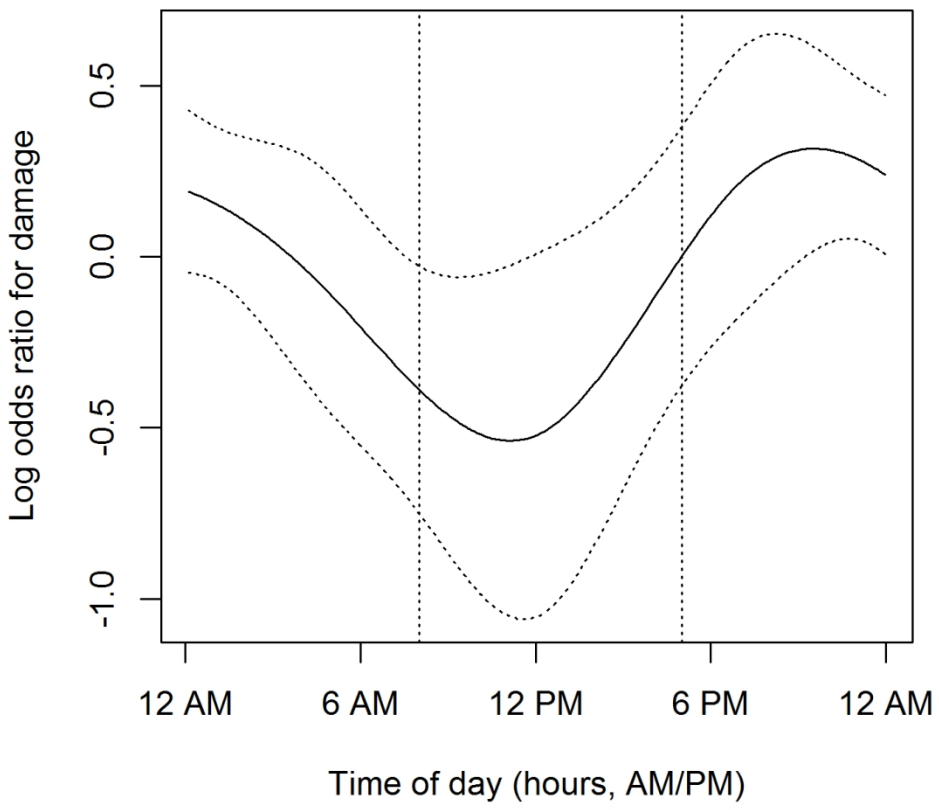

Figure 1. The relationship between starting time of the cold perfusion of the aorta and risk of injury.

127x127mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	1 and 5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
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	*6*
Bias	9	Describe any efforts to address potential sources of bias	10-11 and 12-13
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	6
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	8
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
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	6
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(9)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
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	3

*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.

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.

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Surgical quality in organ procurement during day and night; an analysis of quality forms

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Running title: Surgical quality and time of procurement

Abbreviations:

DCD, Donor after determination of circulatory death

DBD, Donor after determination of brain death

QF, Quality form

Words: 2,438 words

Abstract (250 words)

Objectives

To analyse a potential association between surgical quality and time of day.

Design

A retrospective analysis of complete sets of quality forms filled out by the procuring and accepting surgeon on organs from deceased donors.

Setting

Procurement procedures in the Netherlands are organized per region. All procedures are performed by an independent, dedicated procurement team that is associated with an academic medical center in the region.

Participants

In 18 months' time, 771 organs were accepted and procured in The Netherlands. Of these, 17 organs were declined before transport and therefore excluded. For the remaining 754 organs, 591 (78%) sets of forms were completed (procurement and transplantation). Baseline characteristics were comparable in both day- and evening/night-time with the exception of height (p=0.003).

Primary outcome measure

All complete sets of quality forms were retrospectively analyzed for the primary outcome, procurement related surgical injury. Organs were categorized based on the starting time of the procurement in either day- (8AM–5PM) or evening/night-time (5PM-8AM).

Results:

Out of 591 procured organs, 129 organs (22%) were procured during daytime and 462 organs (78%) during evening/night-time. The incidence of surgical injury was significantly lower during

daytime; 22 organs (17%) compared to 126 organs (27%) procured during evening/night-time (p=0.016). This association persists when adjusted for confounders.

Conclusions:

This study shows an increased incidence of procurement related surgical injury in evening/night-time procedures as compared to daytime. Time of day might (in)directly influence surgical performance and should be considered a potential risk factor for injury in organ procurement procedures.

Strengths and limitations

- Quality of procurement is evaluated by two specialists; once by the procuring and once by the accepting surgeon. (+)
- All procedures are performed by a dedicated, certified procurement team. This ensures a high standard of procurement quality. (+)
- Selection bias in the timing of procurements is minimal because the planning is mainly logistical rather than medical. (+)
- Injury is evaluated in a categorical way (yes/no) to analyze surgical performance in a broad sense. It avoids a loss of detailed information but limits a sub analysis on injuries leading to discarding organs.
- Conclusions may be limited by the number of procured organs. (-)

Introduction

Nights shifts have been shown to pose a higher risk for errors and self-injuries in several medical settings[1–4]. A negative effect of nights shifts might be caused by factors associated with fatigue and circadian rhythm[5] and could also affect surgical performance. The potential relation between timing of procedures and surgical performance, is however not clear. Studies have reported conflicting results[6–10] and timing of procedures might therefore affect patients' safety. The discussion on the topic, has contributed to reforms in working hours for surgical residents in the US, as well as in Europe.

The lack of evidence for a causative relationship between fatigue related factors and inferior performance in surgery is interesting considering the extensive amount of evidence in other fields[11,12]. Although it might hold true that surgical performance is not affected by fatigue or time of day, it could also be a consequence of an insufficiently sensitive measurement of technical proficiency. To measure surgical performance, a negative clinical outcome in patients would be the most obvious endpoint. This has however some limitations. A clinical endpoint might lead to a loss of detailed information because only severe intra-operative injuries are likely recognized for their clinical impact while minor injuries might be missed. Secondly, it is difficult to relate a specific surgical injury to a particular negative outcome in a patient, because not all intra-operative injuries are noticed and negative outcomes are multifactorial and complex. A potential (minor) effect of time of day on surgical performance might therefore not be noticed when solely focussing on clinical outcome measures.

The Dutch digital feedback system on the quality of organ procurement offers an opportunity to analyse surgical performance in detail. We have previously analysed this dataset on procurement related surgical injuries and found a high incidence of non-critical injuries. We did not find a

significant difference between the non-critically injured and intact organs for one year graft survival[13]. In this study, surgical injury is considered as a sensitive proxy of surgical performance. We hypothesize that a relationship is present between surgical performance and time of day.

Methods

Data

We obtained data from the Dutch Transplant Foundation on quality forms filled out from March 2012 until September 2013. It comprises two forms on each individual abdominal organ that is procured and accepted in The Netherlands. One form is filled out by the procuring surgeon after procurement and concurred or commented on by the accepting surgeon in the second form. Detailed information is registered on packaging, perfusion (time/volume/fluid), anatomy and possible injury of vessels or organs. In case of a discrepancy between the procuring and accepting surgeons, remarks of the accepting surgeon were considered leading. Pancreata procured for islet-isolation and organs that were declined before transportation to the accepting center were excluded. No ethical statement was required according to national ethical guidelines. Data are available upon request at the Dutch Transplant Foundation. Permission for this analysis was granted by the national competent authority, the Dutch Transplant Foundation, on April 6th, 2017.

Patient and public involvement

Patients were not involved in the development of the research question or in the design of the study.

Statistical analysis

We accepted the time of cross-clamping the aorta and start of the cold perfusion as starting time of the procedure. For donation after circulatory determination of death (DCD) this is almost at the same time, but for donation after determination of brain death (DBD) this usually is 1 – 2

hours after skin incision. Vascular anatomy of organs was considered to be 'normal' for kidneys when a single artery and vein were observed. For livers and pancreata from the same donor, anatomy was considered normal according to the variable normal arterial anatomy (y/n) in the liver quality form. In case information on the vascular anatomy was missing it was considered to be normal (n=3, 0.5%). All organs were categorized in two groups; daytime (when procured between 8AM and 5PM) or evening/night-time (when procured between 5PM and 8AM). The incidence of injury was dichotomized (yes/no) and compared between both groups using univariate logistic regression with time of day as sole covariate. The analyses were adjusted for potential confounders, statistical significant in univariate analyses, and for known confounders reported in the literature. These factors include body mass index (BMI) and donor type (DCD or DBD)[13–16].

The relationship between injury and starting time of the procedure was visualized as a log odds ratio on a continuous 24 hours' scale by using splines regression. To correct for a possible correlation of injury within donor procedures, sandwich estimators of the standard errors were used. A p-value of <0.05 was considered statistically significant and analyses were performed with SPSS version 22.0 and R version 2.3.3.

Results

During the study period, 771 organs were accepted for transplantation, of which 17 (5 livers, 8 pancreata and 4 kidneys) were declined during procurement and subsequently not transported. For all 754 accepted and transported organs, 591 forms were completed (591/754, 78%) on 133 livers (23%), 38 pancreata (6%) and 420 kidneys (71%). Response rates per organ were respectively 87%, 90% and 75%. There were 148 (148/591, 25%) organs with reported injuries; 36 livers (36/133, 27%), 10 pancreata (10/38, 26%) and 102 kidneys (102/420, 24%). Of all injured organs, 12 (2%) were discarded because of this surgical injury; 1/133 (0.8%) liver, 5/38 (13%) pancreata and 6/420 (1.4%) kidneys ($p<0.001$).

Day and night-time operating hours

With the exception of donor height ($p=0.003$) organs were comparable in demographical characteristics in the daytime and evening/night-time groups in univariate analysis as shown in Table 1.

Table 1. Demographics of the study population (n=591). Only height is different between the two groups (p=0.003).

	Daytime (8AM-5PM) n=129			Evening- and nighttime (5PM-8AM), n=462			
	Mean (SD)	**Median**	**Range**	**Mean (SD)**	**Median**	**Range**	**p-value**
Age	51.8 (15.3)	55	14-76	52.2 (15.6)	55	10-78	0.772
Height	177.4 (7.1)	180	161-198	174.8 (9.4)	175	140-200	**0.003**
Weight	76.6 (13.4)	78	52-120	76.6 (15.1)	77	35-150	0.996
BMI	24.3 (3.6)	24.0	17.6-34.7	25.0 (4.1)	24.7	12.5-46.3	0.080
	n (%)			**n (%)**			
Sex							
Male	75			256 (55)			

	(58)				
Female	54 (42)		206 (45)		0.581
Donortype					
DBD	69 (53)		210 (45)		
DCD	60 (47)		252 (55)		0.106
Aberrant anatomy	32 (17)		129 (28)		0.458

Volume related regional effects that may also impact the risk of surgical injury[13], were not significantly different between both groups (data not shown). During daytime, 129 of 591 organs (22%) were procured and 462 organs (78%) were procured during evening/night-time. There were fewer organ injuries during daytime procurements compared to evening/night time, respectively; 22 organs (17%) and 126 organs (27%) (p=0.016). In the full adjusted model evening/night-time procedures remained an independent factor associated with injury (p=0.029). Of all critically injured organs, 7 out of 12 (60%) were procured in evening/night-time as compared to 5 out of 12 organs in daytime. The distribution of critical injuries (table S1) seems therefore to correspond with the distribution of procurements (figure S1).

Circadian points

Figure 1 shows the increased risk of injury for procedures that start in evening/night-time. The highest risk of organ injury was for procedures starting around 9PM, the lowest risk for procedures starting around 12PM (noon).

Discussion

This study shows a relationship between surgical performance and the starting time of the procurement procedure. A higher incidence of surgical injury is observed during evening/night-time procedures as compared to daytime procedures. This association persists when adjusted for important confounders.

The relation between surgical performance and timing of surgical procedures is often highly confounded. Patients have more complicated and/or acute problems during the night[17]. Also, access to imaging and laboratory testing as well as specialized operating room (OR) nurses and anesthesiologists might be less available during night-time[13]. The study population of this study, abdominal organs from deceased donors, eliminates several of these confounders. Most procedures can generally be scheduled within 6-24 hours regardless of the cause of brain death because these patients are usually hemodynamically stable. A higher number of procurement procedures during evening/night-time therefore seems to reflect issues with OR availability during the day rather than an abundance of emergency procedures. Secondly, abdominal organ procurement is well organized in The Netherlands; each sub region has a 24/7 availability of a self-supporting, certified organ procurement team. Such a team includes, both during daytime and evening/night-time procedures, two dedicated nurses, a dedicated anesthesiologist and two surgeons, of who at least one is certified for procurement procedures according to the national guidelines. This includes the ESOT procurement e-course, a minimum of ten multi-organ procurement procedures followed by an examination by a non-regional procurement surgeon. The certified surgeons are then members of the regional dedicated procurement teams that operate on a 24h basis and are not involved in other clinical activities while on duty. The extensive training to become certified and the absence of other clinical activities when on call,

ensure a high quality of organ procurement and eliminates a major variance in operating staff. In addition, differences in hospital facilities (local vs. academical) should be minimal because the teams are self-reliant and bring own standard supplies for the procedure. In our opinion, this offers a unique setting.

Another strength of this study is the very small difference in baseline characteristics of the day- and evening/night-time groups. Donor characteristics described to be associated with procurement related injury in kidney[14], liver[16] and pancreas[15] procurement procedures (such as: donor age, DCD donor type, BMI, aberrant anatomy and male gender) were not significantly different. Only donor height was different between both groups and so far this factor has not been described to influence the risk of organ injury. The similarity between both groups is likely associated with the planning of procedures; independent of donor characteristics and solely dependent of OR availability. Other relevant variables can therefore be assumed to be equal in both groups since they do not affect or are not affected by the starting time of procedures. This includes non-measured donor associated characteristics, for example previous abdominal surgery, as well as potential differences in reporting injuries when organs were procured by surgeons from the same transplant unit as the transplanting team. Factors that might have been different and might have influenced our results, include volume related regional effects as previously described[13]. The ratio between regions for day- and evening/night-time procedures was however not different (data not shown).

In this study, we evaluated all surgical injury in a strict dichotomous way (yes/no) to analyze surgical performance in a broad sense and to avoid a loss of detailed information. In further studies, it could be of relevance to further specify the definition, type and impact of injury. In the

current data for example, the number of critical injuries –leading to discarding of the organ- (n=12) are insufficient for an adequate comparison in day- and evening/night-time groups.

A limitation of this study is the response rate for complete sets of forms of 80%; a higher response rate might have led to a higher reported number of (critical) injuries. Although the response rate could have been better, it is to be noted, that the current response rate concerns organs on which two forms are digitally filled out by two independent surgeons. This two-way registration can be considered to be precise and objective.

Our results are in accordance with (non-surgical) medical studies that report a negative relation between evening/night-time or fatigue related factors and performance; a higher rate of self-injuries among residents[3] and a decreased proficiency in surgical simulations after night shifts[8]. These results are conflicting with large surgical database studies that show no difference in conversion rates during cholecystectomy or outcome in patients like the occurrence of serious adverse events[6,18]. Rothschild *et al.* on the other hand, found an increased rate of complications during post night-time surgical procedures performed by physicians with sleep opportunities of less than 6 hours[10]. A study on liver transplantation, found that surgical procedures during night-time took longer and were associated with a higher risk of early death, although without any effect on peri-operative complications or long-term survival[19]. Also in kidney transplantation, more peri-operative complications[20] but less technical graft failure[21] were seen in night-time procedures. The latter did not take into account a difference in surgical experience between day- and night-time procedures; night-time procedures are rather performed by consulting surgeons as compared to daytime procedures that are usually performed by (supervised) surgical residents. In the current study however, all procedures were performed by the same group of dedicated surgeons and teams.

These studies seem to report contradictory findings between short term or non-patient outcomes on the one hand and long-term outcome in patients. This observation is reflected in our data; we noticed a higher incidence of surgical injuries during night-time (this study) but no difference in one year graft survival between injured and intact organs in a previous analysis of the same cohort[13]. This indicates that the pathway leading to a negative outcome in surgical patients is complex and multi-factorial and only the most severe surgical injuries might result in clinically measurable negative outcome. To find a significant difference in outcome in patients that can be related to the timing of procedures or 'fitness' of surgeons, higher numbers are probably needed. This study can therefore only assess (technical) surgical performance.

The increased injury rates during evening/night-time operating hours may indicate that surgical performance is affected by time of day. The etiology of this association is however not yet clear. The negative effect of evening/night-time procedures suggests an effect of fatigue related factors. Fatigue was however not measured in this study and should theoretically play a smaller role because procurement teams can rest between procedures and do not participate in other clinical activities when on call. Other mechanisms might however contribute; the surgical injury pattern in this study shows, for example, a remarkable resemblance with circadian rhythm and associated biological hormone levels as observed in chronobiology[22]. To further identify the mechanism behind the higher injury rate during evening/night-time, it will be essential to objectively measure the surgeon's fitness before and after procurement. Current research on the validation and clinical application of such a "Fit to Perform" test is ongoing[23]. It might give an objective tool to evaluate the relation between the fitness of a surgeon and his surgical performance.

We believe this study shows, that evening/night-time procedures might present a suboptimal setting for organ procurement. Although the causal pathway is not yet clear, our results do suggest that time of day should be taken into account to optimize the quality of organ procurement. Theoretically, transplantations in the evening/night-time may also be related to a higher risk of complications. If so, this poses a dilemma because the timing of the procurement also affects the timing of the transplantation. Although a higher risk of complications in transplantations during the evening/night-time has not been described, it seems best to perform the procurement early in the morning. In such a way, it is still possible to subsequently start the transplantation operation that same afternoon. Timing may even be of relevance for other surgical procedures. This would mean that, in the absence of acute pathology, surgeries should be preferably performed during daytime.

Conclusion

This study shows an increased incidence of surgical injury in organ procurement procedures during evening/night-time, as compared to daytime. Time of day might (in)directly influence surgical performance and should be considered a potential risk factor for injury in organ procurements.

Acknowledgements

The authors would like to gratefully acknowledge Cynthia Konijn, Dilesh Kishoendajal and Steffen de Groot (Dutch Organ Transplant Registry) for their efforts in collecting the data.

Figure legends:

Figure 1. The relationship between starting time of the cold perfusion of the aorta and risk of injury.

Supplementary files:

Figure S1. Number of procured organs per time of day (h)

Table S1. Time of the start of the procurement procedure(h) of injured organs that were discarded for transplantation (n=12).

Author contributions:

Dr. De Boer, Dr. Van der Bogt and Dr. Braat hypothesized that a relationship may be present between time of day and the incidence of surgical injury. Dr. Van der Bogt is involved in the Fit to Perform trial currently performed in The Netherlands. Data on procured organs are provided by all six transplanting centers in the Netherlands to the Dutch Transplant Foundation. Permission to use these was granted by delegates from all centers; Dr. Pol (Groningen), Dr. De Jonge (Rotterdam), Dr. Dejong (Maastricht), Dr. Nijboer (Leiden) and Dr. Van der Vliet (Nijmegen). Data were then obtained via the Dutch Transplant Foundation where Mrs. Ooms-De Vries and Mrs. Haase-Kromwijk were involved. Data were analysed and statistical analysis was performed and interpreted by Dr. De Boer, Dr. Van der Bogt, Dr. Braat and Prof. Putter of the Statistical Department. The manuscript was then drafted by Dr. De Boer, Dr. Van der Bogt, Dr. Braat and Prof. Putter. The draft manuscript was critically revised by all involved.

Funding and Competing Interests Statement:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. There are no conflicts of interest.

Data sharing agreement

Data are available upon request at the Dutch Transplant Foundation. Permission for this analysis was granted by the national competent authority, the Dutch Transplant Foundation, on April 6th, 2017.

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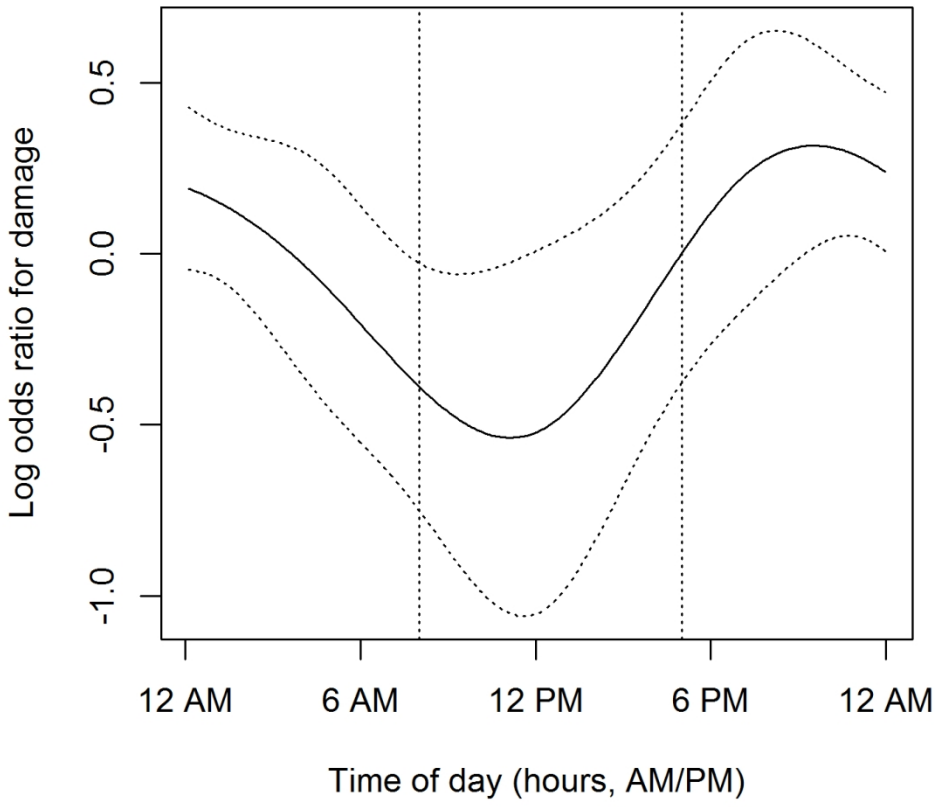

The relationship between starting time of the cold perfusion of the aorta and risk of injury.

127x127mm (300 x 300 DPI)

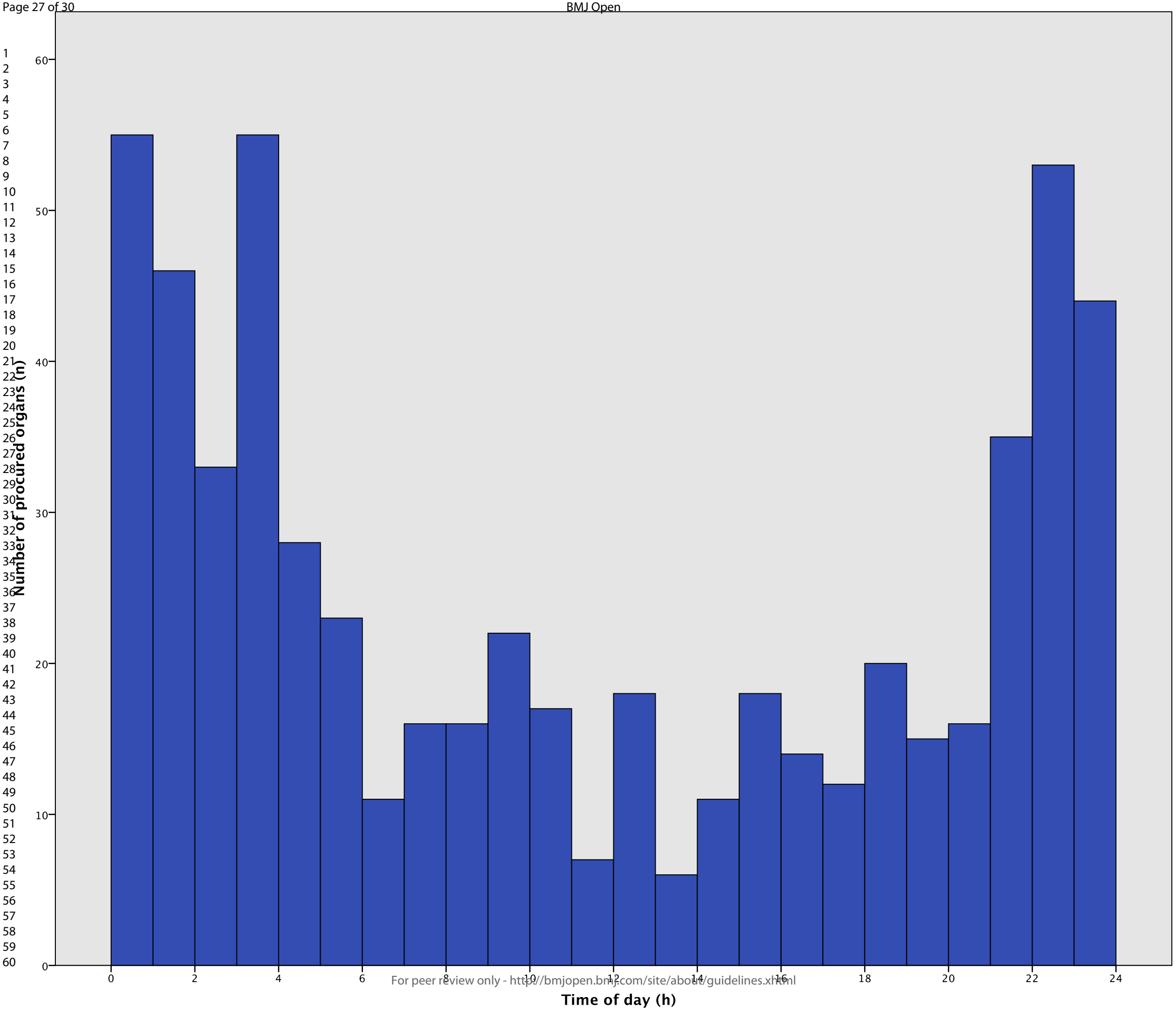

Table S1

Organ	1	2	3	4	5	6	7	8	9	10	11	12
Time	1.1h	2.4h	3.0h	3.0h	3.0h	4.3h	12.4h	14.3h	15.2h	15.2h	15.2h	22.5h

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	1 and 5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
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	*6*
Bias	9	Describe any efforts to address potential sources of bias	10-11 and 12-13
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	6
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	8
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	8
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	6
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(9)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
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	3

*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.

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.