

## ORIGINAL ARTICLE

## RAMADAN-ASSOCIATED CIRCADIAN CENSUS VARIATION IN A BUSY MIDDLE EASTERN EMERGENCY DEPARTMENT

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**Background:** An important goal for the Emergency Department operations is planning for changes in patient volume and assuring staffing accordingly. We hypothesized that understanding the Emergency Department census changes during the month-long Ramadan holiday each year could facilitate operations planning for Emergency Department's serving a largely Muslim population. **Methods:** This was an observational study conducted at an academic centre, over 83 weeks of analysis that included two Ramadan months (those occurring during 2016 and 2017). The data was from an electronic medical record that records presentation time as well as age, sex, nationality, and acuity. Chi-square and median-differences testing ( $p < .05$  defining significance) were used to compare overall patient characteristics between cases seen during Ramadan vs. non-Ramadan. **Results:** For the 83 study weeks, the Emergency Department volume was 689,140 (annualized volume 431,750). Graphic depiction of weekly census showed Ramadan-associated census impact varied markedly over the course of a day's 24 hours. Statistically significant hourly census increase (of up to 83%) or decrease (of as much as 50%) were identified for 21 of 24 hours of the day. Ramadan was not associated with change in patient age or proportion of high-acuity cases. However, it was associated with increase in proportion of males, paediatrics, and Qatari national's patient visits. **Conclusions:** As compared to non-Ramadan baseline, Ramadan was associated with substantial changes in overall census and in proportions of various patient subgroups. Therefore, Emergency Department's serving large Muslim population should undertake studying major operations changes that can be expected for the month.

**Keywords:** Ramadan; Emergency department operations; Emergency department

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## INTRODUCTION

Emergency Department (ED) operations planners are constantly striving to optimize efficiency of care.<sup>1,2</sup> Of the many factors used as measures of care efficiency, most are influenced by patient volume.<sup>3–6</sup> Therefore, prediction of patient volume changes is an important part of ED operations planning.

One important source of ED volume changes that has long-known predictability is the census fluctuation surrounding short holiday periods.<sup>7</sup> For longer holiday periods, such as the 30-day Ramadan period, there are fewer data about ED census effects. Extant information suggests potential importance of operations changes associated with Ramadan, although the current evidence base is not definitive.

As long ago as 1994, a group from London identified an increase in the number of Muslim Ramadan observers presenting to the ED during the fasting weeks, as compared to the few weeks preceding and following.<sup>8</sup> Subsequent reports have presented and debated medical points regarding effects of prolonged fasting alternating with consumption of large meals. Entities with suggested Ramadan associations include (but are not limited to) headache, hypertension, acute coronary syndrome (ACS), ureteral colic, various metabolic abnormalities, and even road traffic accidents (RTAs).<sup>9,12</sup>

Despite the extent of discussion and debate over Ramadan's association with medical problems, there has been relatively little rigorous focus on the holiday month's circadian census effects. The goal of this report was to assess ED census and demographics changes associated with Ramadan in a busy Middle Eastern ED. The investigators' intent was to build on the current evidence base by assessing round-the-clock census changes seen during Ramadan.

## MATERIAL AND METHODS

This was an electronic medical record (EMR)-based, non-interventional, observational study in which no patient interaction occurred between investigators and patients. No patient identifiers were recorded, and the study was approved by the institutional research and ethics board.

The study ED is the national tertiary care centre of the State of Qatar. During the study period, the ED had a weekly volume median of 8270 patients (range: 7375–9472). All areas of the study ED use the same EMR, First Net Cerner Millennium (Cerner, Kansas City, Missouri, USA) which was deployed in May 2016. The EMR implementation was timed to coincide with a late-spring period that is historically less busy in the study ED. In 2016, this late-spring period also coincided with the period of approximately two months before Ramadan.

The study time frame thus ran from the month prior to Ramadan start 2016, through the end of December 2017.

Study data arose from ED visits May 2016 through December 2017, with visits occurring during the 60 days of Ramadan (i.e., 30 days each year) were classified as Ramadan visits; other visits were non-Ramadan cases.

The patient demographics that were assessed as part of this study included sex, paediatric (age <15 years) status, and nationality. Nationality was dichotomized: patients were classified as either study-country nationals or expatriates.

Study data were downloaded from the EMR and transferred to the software package Stata (version 15MP, Stata Corp, College Station, Texas) which was used for all graphing and statistical analysis. Statistical significance was set at  $p < .05$  and confidence intervals (CIs) were calculated at the 95% level.

For comparison of proportions (e.g. % male cases during Ramadan vs. non-Ramadan), descriptive results were reported with binomial exact CIs and significance was assessed with chi-square testing. Continuous data, which were identified as non-normal using Stata's skewness-kurtosis procedure, were described with median and interquartile range (IQR) and analysed with non-parametric Kruskal-Wallis testing and calculations of median inter-group differences (Stat's *cen dif* procedure).

Circadian analysis commenced with categorizing all ED presentations by clock-hour of registration. Hour 1 was defined as indicating patient presentation between midnight and 0059. Hour 2 indicated registration in the 0100–0159-time frame, Hour 3 0200–0259, and so on through Hour 24 (registration 2300–2359).

After constituting the study dataset such that the hourly census for a given circadian hour could be tracked for every day of the study, data were tabulated for each of the day's 24 hours with regard to Ramadan-associated changes in overall census and in the patient characteristics of interest. Because of the large size of the dataset, there was a high potential for statistical testing to identify operationally unimportant census changes as "significant." Therefore, operationally important census changes were defined *a priori* as Ramadan-associated increases or decreases in census that exceeded 10% of non-Ramadan baseline.

Data were also assessed with scatterplots and locally weighted scatterplot smoothing (lowess), which generates a non-parametric trend line that requires no assumptions about distribution of the data. The lowess trend function was used to afford easy visualization of each circadian hour's ED census changes over the course of the study period.

Lowess lines were used to facilitate comparisons across different circadian hours.

Visualization of similar trend lines across adjacent hours allowed for grouping of circadian hours by Ramadan-associated census effects. Other graphic techniques used to portray the varying intra-day effects of Ramadan included radar plotting and plotting of 95% CIs for median census changes from non-Ramadan to Ramadan days. Graphic and tabular methodologies were combined to use different and complementary techniques to portray the complex changes seen during Ramadan.

## RESULTS

Descriptive information on the 689,140 study ED cases is shown in table-1. The table also shows the univariate comparisons between demographic characteristics of the Ramadan vs. control days.

The right-most column in table-1 indicates whether the row characteristic was statistically significantly different between Ramadan and control periods. For example, daily census was lower during Ramadan to a degree that was statistically (and operationally) significant: median decrement in daily census during Ramadan was 126 (95% CI 101–140). By skewness-kurtosis testing, both the Ramadan histogram ( $p=.54$ ) and the non-Ramadan histogram ( $p=.14$ ) were found to have normal distributions.

For each of the 24 circadian hours, the median difference between hourly censuses for each hour, for Ramadan vs. control period, is shown in table-2. The changes in census associated with Ramadan as compared to non-Ramadan days are further outlined, which depicts for each hour, the % increase (or decrease) in ED census seen during Ramadan.

The results tabulated in tables-2 and 3 were used to generate graphic display of trends in census during Ramadan. For each circadian hour, a scatterplot was generated that included a lowest trend line. Three scatterplots are as examples for circadian hours with positive, negative, and no census variation during Ramadan. In each scatterplot, the circadian hour numeral markers represent a single day's count of ED cases presenting during that clock-hour.

In order to facilitate intuitive clock-based depiction of the circadian changes in hourly census during Ramadan, a radar plot was generated (Figure-1). The plot's radial grid is intended to mimic a 24-hour clock, with plot-lines that move towards or away from the clock's centre with decreasing or increasing census, respectively.

The figure-1 plot depicts the non-Ramadan circadian census variation (solid red line) of standard ED operations at the study centre: ED census is highest in the mid-morning hours and lowest in the early-morning hours (with lowest hourly census for the presentation time frame 0200–0259). The figure demonstrates that for Ramadan, the peak hours for daily census occur between approximately 2000 and midnight (study hours 21

through 24). Figure-1 indicates which of the day's hours are affected most by Ramadan, and also shows whether Ramadan is associated with a particular presentation hour's census increasing (i.e. dashed line is outside solid line) or decreasing (dashed line is inside solid line). Finally, the degree of gap between the dashed and solid lines indicates the magnitude of hourly census difference between Ramadan and non-Ramadan time frames.

The final analysis steps consisted of assessment as to whether there were differential circadian effects, as compared to the overall effects just discussed, for the study's four main patient characteristics (high-priority cases, males, paediatrics, and Qatari nationals).

The intent of this analysis was to explore whether the four patient types' Ramadan-associated circadian census variations differed from the Ramadan-associated census variations seen in the overall ED population. The analytic approach was two-part. First, Ramadan-month changes in the four groups' circadian census were tabulated.

Next, for each of the four groups the median circadian census variations' 95% CIs were plotted against the background of the 95% CI for overall circadian census variation. For Figure-1 interpretation, if the bars representing the 95% CI for census change from non-Ramadan to Ramadan crossed zero, there was no statistically significant change in that circadian hour's

census for that group. Similarity between Ramadan-associated circadian census trends for a subgroup was suggested if that group's census bars moved in tandem with the overall circadian census changes (dashed line). Tracking was clearly present for males, and there was identifiable (attenuated) matching of overall census trends for subgroups of paediatrics and Qataris. There was little if any Ramadan-associated change in circadian census of high-acuity cases.

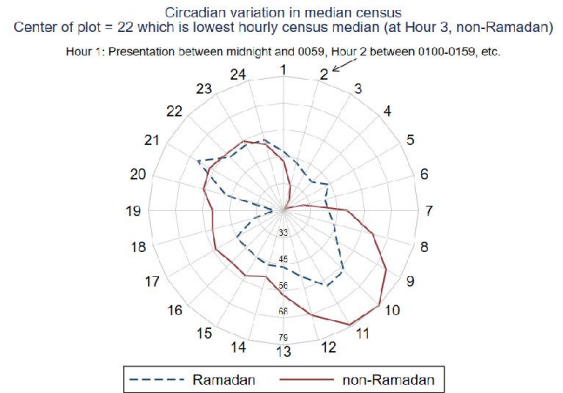
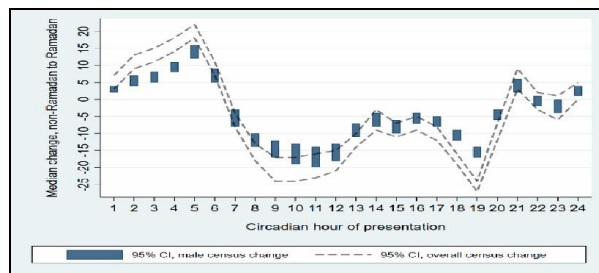
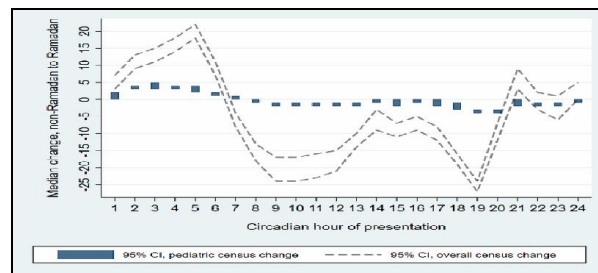


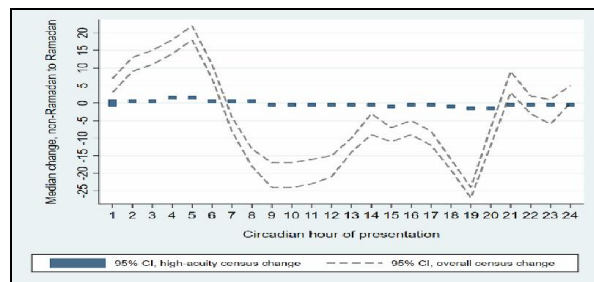
Figure-1: Circadian radar plot of emergency department census by Ramadan/non-Ramadan time frame



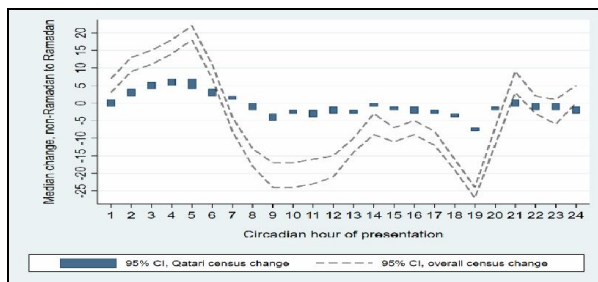
(a) 95% confidence interval (CI) for median census change from non-Ramadan to Ramadan: Male patients



(b) 95% confidence interval (CI) for median census change from non-Ramadan to Ramadan: Pediatric patients



(c) 95% confidence interval for median census change from non-Ramadan to Ramadan: High-acuity patients



(d) 95% confidence interval (CI) for median census change from non-Ramadan to Ramadan: Qatari patients

Figure-4: Ramadan vs. non-Ramadan circadian variation: high-acuity cases, pediatrics, Qataris, and male cases

**Table-1: Emergency Department cases seen during the study period (p value for Ramadan vs. non-Ramadan)**

Parameter	Overall	Ramadan	Non-Ramadan	p
Age, median (IQR)*	32 (25–41)	32 (25–42)	32 (25–41)	.74
Male, % (95% CI)**	69.8% (69.7–70.0%)	70.0% (69.9–70.1%)	68.5% (68.1–68.8%)	<.001
Qatari nationality, % (95% CI)	19.2% (19.1–19.3%)	19.7% (19.4–20.0%)	19.1% (19.0–19.2%)	.001
Paediatric (age <15), % (95% CI)	10.5% (10.4–10.5%)	10.8% (10.6–11.1%)	10.4% (10.3–10.5%)	.001
Higher-acuity triage, % (95% CI)	6.9% (6.8–7.0%)	6.7% (6.5–6.9%)	6.9% (6.9–7.0%)	.056
Daily census, median (IQR)	1192 (1125–1264)	1090 (1031–1133)	1203 (1142–1273)	.0001

\*IQR – interquartile range. \*\*CI – confidence interval

**Table-2: Median census differences for each circadian hour, Ramadan vs. non-Ramadan**

Hour	Median (IQR)* non-Ramadan census	Median (IQR) Ramadan census	Median (95% CI) ** census change from non-Ramadan to Ramadan
1 (0000–0059)	43 (37–49)	47 (43–53)	5 (3–7)
2 (0100–0159)	33 (29–40)	43 (41–49)	11 (9–13)
3 (0200–0259)	27 (23–31)	40 (35–44)	13 (11–15)
4 (0300–0359)	22 (19–26)	39 (34–45)	16 (14–18)
5 (0400–0459)	24 (20–28)	44 (38–49)	20 (18–22)
6 (0500–0559)	31 (26–36)	40 (36–44)	9 (7–11)
7 (0600–0659)	49 (41–58)	41 (36–47)	-6 (-4 to -8)
8 (0700–0759)	61 (52–69)	44 (37–49)	-16 (-18 to -13)
9 (0800–0859)	72 (61–82)	48 (42–55)	-21 (-24 to -17)
10 (0900–0959)	79 (67–92)	58 (48–63)	-20 (-24 to -17)
11 (1000–1059)	78 (67–88)	59 (47–63)	-20 (-23 to -16)
12 (1100–1159)	68 (60–78)	51 (44–56)	-18 (-21 to -15)
13 (1200–1259)	58 (51–65)	46 (42–49)	-12 (-14 to -10)
14 (1300–1359)	51 (46–57)	46 (39–55)	-6 (-9 to -3)
15 (1400–1459)	54 (48–60)	45 (40–51)	-9 (-11 to -7)
16 (1500–1559)	53 (47–59)	44 (41–50)	-7 (-9 to -5)
17 (1600–1659)	55 (49–61)	45 (40–49)	-10 (-12 to -8)
18 (1700–1759)	53 (48–59)	35 (31–39)	-18 (-19 to -16)
19 (1800–1859)	52 (47–57)	26 (22–30)	-26 (-27 to -24)
20 (1900–1959)	57 (51–63)	47 (42–52)	-9 (-12 to -7)
21 (2000–2059)	58 (52–64)	64 (57–69)	6 (3–9)
22 (2100–2159)	56 (50–61)	54 (50–61)	0 (-3 to 2)***
23 (2200–2259)	56 (51–62)	54 (46–59)	-3 (-6 to 1)***
24 (2300–2359)	51 (46–57)	53 (50–57)	3 (0 to 5)***

\*IQR – interquartile range. \*\*CI – confidence interval. \*\*\*95% CI for estimates for median Ramadan-associated census change included 0 (i.e. not significant)

**Table-3: Median census differences for each circadian hour, Ramadan vs. non-Ramadan**

Clock Hour(s)	Relation to sunrise/sunset	Notes
1830	Sunset	Ramadan commences at sunset on 1 <sup>st</sup> day of holy month
1900–2000	Initial hours after sunset	Breaking of Ramadan fast occurs each day after sunset; evening ( <i>Maghrib</i> ) prayer occurs at this time
2030–2200	2 hours after sunset	<i>Isha</i> and <i>Tarawih</i> (night) prayers
2200–0200	Late evening, 4 hours after sunset	Brief period of rest at night
0200–0400	Early morning, 8 hours after sunset	<i>Sahoor</i> (early breakfast), prayers ( <i>Tahajud</i> and <i>Fajr</i> )
0400–0500	1 hour prior to sunrise	Preparation for day of fasting
0500–1200	After sunrise	Working (hours are reduced; workday for many ends at noon)
1200–1700	7 hours after sunrise	Prayers ( <i>Zohar</i> and <i>Asr</i> ) and a brief period of rest
1700–1830	12 hours after sunrise	Preparation for breaking fast ( <i>Iftaar</i> ) and prayer ( <i>Maghrib</i> )

**DISCUSSION**

There have been previous ED studies assessing patient demographics and census changes during the Muslim holy month of Ramadan. The results of those studies are informative, providing a sound basis upon which this study’s authors hope to build more complete understanding of the ED impact of Ramadan. A brief assessment of the extant literature aids in framing the current study’s results.

A 2005 report from Turkey focused on disease patterns seen during Ramadan and found that most presentation frequencies—exceptions were hypertension and headache—were not altered during the fasting month; demographics were also generally

unchanged.<sup>13</sup> These results of no association between Ramadan and ED volume or demographics were reported 5 years later by another group of Turks.<sup>14</sup>

In 2006, a group from Jordan found that RTAs were decreased during Ramadan.<sup>10</sup> However, a decade later a more detailed Pakistani analysis found that while the overall number of RTAs did not change in Ramadan, there were alterations in circadian clustering of RTAs. The incidence of RTAs was highest after the post-sunset breaking of the fast, and after the *Tarivah* prayer a few hours later.<sup>11</sup>

The Pakistani study was important because of its finer focus on presentation hours, not just Ramadan vs. non-Ramadan comparisons. Whereas

analyses such as a third Turkish study (from 2010)<sup>14</sup> that reported no association between Ramadan and ED visit numbers are helpful, they are limited by not assessing for differential effects of Ramadan depending on time of day. More recent literature has begun to address that question.

Two 2016 studies and one from 2017 have shed light on the circadian variation of ED operations effects of Ramadan. The first 2016 study, from Saudi Arabia, dichotomized four years of ED visits ( $n = 226,075$  patients) into day shift (0700–1859) or night shift (1700–0659). The Riyadh group found that while acuity did not change during Ramadan, the holiday month saw a reversal of the non-Ramadan day-to-night ratio of 60:40.<sup>15</sup>

Also, in 2016, a group based in Abu Dhabi published their experience over four years of ED visits. Assessed by median arrivals per day, Ramadan period's adult visits were lower (148–143) but neither statistically nor operationally significant; daily paediatric visits were significantly decreased during Ramadan (43 vs. 57). The authors found that after the fast was broken (in Abu Dhabi over the study's years, around 1800) there were a few hours of markedly decreased census, with a reversal of the trend by 2030 (i.e., similar to the RTA results reported by Mehmood).<sup>11,16</sup>

A 2017 study from Beirut assessed a total of 3536 cases over three years, comparing Ramadan months' data to visits one month pre- and one-month post-Ramadan. During non-Ramadan months, daily ED volume was higher (146) as compared to daily volume during Ramadan (129). These authors pointed out an important limitation to many Ramadan studies: actual fasting status was not known, and Ramadan calendar timing was simply a surrogate for presumed fasting of much of the population.<sup>17</sup>

In summary, the existing literature paints a varying picture of Ramadan's effects on ED census, with both census and demographics being reported to be altered or unaltered. The reasons for lack of definitive answers could, of course, be geographic: Ramadan may have different effects in different places. However, the non-agreement of current literature could be due partly to a combination of coarse parsing of circadian hours<sup>15</sup> and partly due to power limitations inherent to low hourly study numbers due to low overall census or restricted focus to certain diseases.<sup>11,16</sup>

The questions left without definitive answers in the existing evidence base comprise the basis for the current study. The three main such questions addressed in this analysis are:

1. In a large-volume ED serving a Muslim population, what census and demographics shifts are observed during Ramadan as compared to the

rest of the year?

2. What differential census effects are seen during Ramadan, at different times of the day?
3. Are Ramadan's census effects the same for ED subgroups demarcated by sex, acuity, age, and nationality?

Before considering this study's results, some methodological flaws must be acknowledged. First, the study goal was to assess ED-visit changes associated with the Ramadan time frame. The study did not include assessment of patients' religion or observance of Ramadan (e.g. fasting during daylight with breaking of the fast after sundown). However, the patterns observed in this analysis could be useful for operations planning regardless as to whether individual ED patients are observing the holiday.

Second, the data that form the basis for this study come from an EMR. EMR-based studies, while attractive for objectivity and non-biased information, have potential disadvantages and the possibility of flawed data should be acknowledged.<sup>18–20</sup> Since the same EMR was used throughout the study, it seems unlikely that any systematic errors were introduced (i.e., for Ramadan vs. non-Ramadan data quality) that would change results.

Third, the finding of little difference in Ramadan-associated findings with respect to high-acuity vs. lower-acuity census (Figure 4c) should be interpreted in light of the significant information loss incurred by collapsing a five-level triage acuity score into two levels. Collapsing of the triage levels was necessary due to separate triage systems being in use during the study period, but the methodology prevented assessment of important changes in census within the collapsed acuity categories (e.g. whether Ramadan was associated with increase in CTAS 4 vs. CTAS 5 census).

One study issue is related to the large size of the dataset, which was beneficial in allowing high power to detect circadian census differences. The study's high power had the drawback of resulting in many findings of statistical significance, which were of questionable operations relevance. The *a priori* change of 10% census change was selected by the authors, but readers should judge for themselves whether the % changes observed in ED census would be relevant to their department.

A final point before moving to detailed consideration of the study results is that the timings should be considered with respect to daylight or night-time, rather than actual clock times. Ramadan behaviours are guided by timing of daylight, not by a specific clock-hour. Ramadan observance will have varying clock-hours even in the same year, for locations with different daylight/night-time hours. Furthermore, the actual calendar occurrence of

Ramadan changes annually. In 2016, Ramadan commenced on 7 June and ended 6 July; 2017 Ramadan timing was 27 May through 25 June. For both years in the current study, sunrise occurred during Hour 5 of the day (i.e. between 0400 and 0500) and sunset occurred during Hour 19 (between 1800 and 1900). The study results will be presented by clock-hour but in order to optimize external validity key results should be considered in context of sunrise/sunset.

With the limitations above in mind, the study provided potentially useful insight into Ramadan's effects on ED census. The overarching finding was that Ramadan saw a census change that was statistically significant and operationally relevant. To put results into perspective, the investigators' study centre median Ramadan-period daily census *decrease* approached to the overall daily volume of many EDs.<sup>17</sup> The census findings have clear implications for possible shifting of resources.

The main demographic results with respect to Ramadan vs. non-Ramadan time periods were that age did not change, but patients were more likely to be male, paediatric, and Qatari. The percent changes were not large for these three variables, but they are still important for EDs that triage cases based on both acuity and demographics. For example, a Ramadan-associated census change of just 3–4 more paediatric cases per hour can have substantial effect on the tasking of physicians and nurses who see children.

The fourth patient characteristic assessed for changes during Ramadan was the proportion of highest-acuity cases. The percent of these cases did not change significantly during Ramadan, but the overall analysis CIs just failed to overlap (Table-1), indicating strong possibility that with more cases in the Ramadan group (e.g. extension of analysis to include a third Ramadan month) the proportional decrease in highest-acuity cases would become statistically significant.

Consideration of the highest-acuity cases provides a useful springboard to move to importance of assessing Ramadan's effects through a circadian lens. As just mentioned, the overall results suggestion was that there was a decrease in highest-acuity cases during Ramadan. However, for the 0300–0500-time frame – the “middle of the night” during which ED coverage is often thinnest—the median number of highest-acuity cases *rose* during Ramadan. The rise was small, with the 95% CI for the increased *n* of CTAS 1 & 2 cases ranging from 1 to 2, but these high-intensity cases can have significant effects on manpower needs. Thus, even for the patient characteristics for which there were no overall census changes during Ramadan, there are possibilities that

specific hours' changes should be considered by operations planners.

It was not just the highest-acuity cases that rose in census during Ramadan's night shifts. The time period of 0300–0500 was characterized by the most marked census increases (73–83%) seen during any of the day's 24 hours. With the commensurate decrease in census during the opposite half of the day (i.e., 1700–1900 census decrease of 34–50%), the normally heavier daytime ED census equalizes with that of the night-time during Ramadan. The radar plot (Figure-1) is illustrative of an essentially equal patient-load distribution across daytime and night-time hours, as seen by the general symmetry of Ramadan-period ED census on either side of a line drawn across the radar plot from Hour 5 to Hour 17.

As previously noted, the detailed analysis of the current study's data is only helpful if they can be applied in the context of a Ramadan time frame that changes with varying time zones, latitudes, or Ramadan time of year. In the study setting, Ramadan occurred during the summer, at latitude in which sunrise occurred between 0400–0500 and sunset between 1800–1900. For these hours of sunrise/sunset, the corresponding Ramadan activity times in the study country are shown in table-3.

Ramadan practices and timings may not be identical in all regions. However, the general patterns for Ramadan observance tend to be similar. For those trying to frame the findings of the current study in the context of Ramadan at other timings, the table-5 information should be helpful. For instance, the marked census decreases during hours 18 and 19 in the current study can likely be extrapolated to a marked decrease in ED census during the initial two hours after sunset. Similarly, the spike in census toward the end of the night time in Ramadan (hour 5 in the current study) can likely be generalized to be likely during the last hour or two prior to daybreak.

Even focusing solely on the operations facets of Ramadan, there is much to be learned and much for which EDs should be prepared. The Ramadan-period ED length of stay (LOS) in Abu Dhabi study was 7% shorter for adults and 20% shorter for paediatric cases.<sup>11,16</sup> But in Beirut, despite decrease in volume the LOS was nearly 50% longer.<sup>17</sup> Further investigation should focus on the nature and effectiveness of specific Ramadan-period ED operations manoeuvres (e.g. increasing night-shift coverage).

## CONCLUSION

At the study site, there were substantial census changes during Ramadan, and those changes exhibited marked circadian variation. There were also important patient-characteristics changes that varied

with circadian hour. Since the Ramadan period accounts for a substantial portion of the year, EDs that serve a large population of Muslims are well-advised to consider the circadian volume changes. This study's methodology and results are offered as aids to EDs that would benefit from Ramadan-related operational planning.

## AUTHORS' CONTRIBUTION

SAT: Conceived the study and wrote the proposal. KB: Critical appraisal and manuscript writing. DWJ: Collected and analysed the data. SAP: Statistical analysis, manuscript writing. SHT: Statistical analysis, manuscript writing and overall supervision of the project.

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