Are registered nurses ready to take care at the end-of-life: crossectional survey

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Abstract

Background: End-of-life care is provided in a variety of healthcare settings, not just palliative care hospitals. This is one reason it is very important to assess all the obstacles to end-of-life care and to provide safe and quality services to patients. The main purpose of this study was to examine attitudes faced by registered nurses in providing end-of-life care and to explore obstacles and supportive behaviors for nurses.

Methods: A descriptive, correlational design was applied in this study. Cross-sectional survey of 1320 registered nurses within 7 hospitals in Lithuania.

Results: Registered nurses working in the three different profiles emphasized safe and effective care and the importance of meeting the patient's spiritual needs at the end of life. The main obstacles assigned by nurses caring for patients at the end of life were angry family members, the inadequate understanding of nursing care by the patient's relatives; family members' inadequate knowledge about the situation and lack of time to talk to patients about their wishes, lack of nursing knowledge to deal with the bereaved patient's family, lack of evaluation of nurses' opinions, and the evasion by physicians to talk about the diagnosis and their over-optimistic view of the situation.

Conclusions: Spiritual needs were identified by nurses as the primary needs of patients at the end of life. Family-related obstacles remain one of the main obstacles to end-of-life care. Also, the behavior of physicians and their relationship with nurses remains one of the most sensitive issues in end-of-life care.

Introduction

Increasing life expectancy, often with multiple illnesses that require complex anesthesia or interventions (hospitalization), also require end-of-life (EOL) care (1). Nurses, physicians, and allied health professionals agree that EOL care should be provided to patients in palliative care units or hospitals where staff have sufficient knowledge of EOL care (2). However, EOL care is provided in a variety of healthcare settings, not just palliative care hospitals. And that is why it is very important to assess all the obstacles to EOL care and to provide safe and quality services to patients. Therefore, providing EOL care in any setting can be challenging (3). Nurses play a key role in EOL care, and their approach to patient EOL care and preparedness is an important factor in ensuring quality and patient-friendly services (4, 5).

Factors that influence the care provided to terminal or dying patients may be nurses’ attitudes towards death (6). According to Roodaet al., “Determinants of attitudes toward death and dying are not only cultural, societal, philosophical, and religious belief systems, but also personal and cognitive frameworks from which individual attitudes toward death and dying are formulated and interpreted” (1999, p 1683) (7). Therefore, nurses’ personal feelings can also be manifested in the way they cope with dying patients. Patients’ deaths often lead to anxiety and undesirable attitudes among nurses, which can influence the quality of patient care. In this study of 403 nurses, Rooda et al. revealed that nurses who felt fearful of a dying patient had a less positive attitude towards patients who were dying. Communication with palliative and terminally ill patients might reflect a nurse’s attitude.

In general, nurses felt discomfort when talking about EOL issues with patients and their loved ones. Based on the scientific literature, this trend is similar in many cultures (8, 9, 10). Researchers revealed that nurses did not feel ready to discuss EOL issues with patients because EOL care was emotionally distressing and required a lot of specific knowledge (8). Therefore, communication with patients was hard work, and nurses expressed a desire to do something else (11). Researchers emphasized that positive nurses’ attitudes in caring for dying patients can be influenced by nurses’ demographic characteristics, experience, and previous education. Nurses with greater experience in dealing with dying patients felt more confident and had a more positive attitude in providing EOL care (12, 13). Thus, the provision of quality EOL care requires knowledge of nurses’ attitudes towards end of life care and readiness to provide this care.
Aim - The main purpose of this study was to examine the attitudes faced by registered nurses in providing EOL care and to explore obstacles and supportive behaviors for these nurses.

Methods

Research design

A descriptive, cross-sectional, correlational design was applied in this study.

Sample

Registered nurses (RNs) were recruited from seven large municipal multi-profile hospitals representing Lithuania. There are approximately 22,500 RNs in Lithuania, and 2,560 work in these hospitals in all unit types (surgical, therapeutic, and intensive care). A study sample of 2,560 was based on a 95 percent confidence interval and a 5 percent error probability (14). For this study, 1,310 RNs were selected to participate. This population of RNs served as the same pool from which a different sample was drawn for another study (15).

Instruments

Nurses' readiness to care for patients at the EOL and attitudes toward their care were assessed using the Questionnaire of Helps and Obstacles in Providing End-of-Life Care to Dying Patients and Their Families (16). The questionnaire was validated and verified in a previous study conducted by the authors (17). Respondents were able to choose the answer options according to a Likert scale with 1 = no help/not an obstacle to 5 = extremely intense help/extremely large obstacle. Socio-demographic characteristics, such as age, gender, employment, current work place, and length of current employment were also collected.

Cronbach's alpha for the questionnaire was established at 0.86, meeting the requirement for acceptance. Similar questionnaires have been used in studies with Oncology departments in Lithuania and Intensive care departments in Spain and the United States (US) (17, 18, 19).

Data collection

Questionnaires were distributed to nurses (face-to-face) by one of the authors at the hospitals during the months of September to November 2017. During the study, 1,320 questionnaires were distributed; 1,180 questionnaires were returned of which 1,055 were satisfactorily completed (response rate 79.9%).

Data analysis

Survey data were analyzed using SPSS for Windows 19.0 (SPSS Statistics for Windows) (20). The level of significance selected for testing data points was established at p ≤ 0.05, meaning the difference was statistically significant. Descriptive statistics were used to calculate the average values of the variables within a 95% confidence interval. The mean and standard deviation of the scores were calculated.

Ethical considerations

The study was approved by the Bioethics Committee at the Lithuanian University of Health Sciences. Hospital administrations were informed of the research goals. Verbal informed consent was obtained from each participant following an explanation of the research study goals during the face-to-face recruitment process. Nurses had the right to refuse participation in the study without penalty. The confidentiality of the respondent was assured and anonymity was maintained. All data were summarized and reported only in the aggregate.

Results

Sample Characteristics
Sociodemographic characteristics are described in Table 1. The average age of RNs participating in the study was 45.8 ± 9.85 years, and the average length of service was 23.4 ± 11.09 years. The majority of respondents were married (N = 668, 63.3%) and worked part-time (N = 786, 74.5%) in mixed shifts (N = 716, 67.9%). Almost half had completed medical college (N = 495, 46.9%). Of all RNs, 49% (N = 516) worked in the internal medicine department, with 32.6% (N = 344) in the surgery department, and 18.4% (N = 195) in the intensive care department.

| Characteristic | N | %   | Kaunas | Klaipeda | Panevėžys | Alytus | Marijampolė | Vilnius | Šiauliai |
|---------------|---|-----|--------|---------|-----------|--------|-------------|---------|---------|
| **Age, years**|   |     |        |         |           |        |             |         |         |
| to 44 years  | 349 | 33.1 | 30 (29.4%) | 26 (26.8%) | 85 (30.6%) | 11 (12.8%) | 15 (22.4%) | 79 (51.0%) | 103 (38.1%) |
| 45 to 50 years | 374 | 35.5 | 38 (37.3%) | 30 (30.9%) | 100 (36.0%) | 32 (37.2%) | 32 (47.8%) | 49 (31.6%) | 93 (34.4%) |
| 51 years and older | 332 | 31.5 | 34 (33.3%) | 41 (42.3%) | 93 (33.5%) | 43 (50.0%) | 20 (29.9%) | 27 (17.4%) | 74 (27.4%) |
| **Educational preparation** |   |     |        |         |           |        |             |         |         |
| Higher University Education | 115 | 10.9 | 15 (14.7%) | 21 (21.6%) | 24 (8.6%) | 3 (3.5%) | 6 (9.0%) | 27 (17.4%) | 19 (7.0%) |
| College | 940 | 89.1 | 87 (85.3%) | 76 (78.4%) | 254 (91.4%) | 83 (96.5%) | 61 (91.0%) | 128 (82.6%) | 251 (93.0%) |
| **Department/ Unit** |   |     |        |         |           |        |             |         |         |
| Surgery department | 344 | 32.6 | 27 (26.5%) | 31 (32.0%) | 79 (28.4%) | 17 (19.8%) | 24 (35.8%) | 79 (51.0%) | 87 (32.2%) |
| Intensive Care department | 195 | 18.5 | 14 (13.7%) | 16 (16.5%) | 53 (19.1%) | 18 (20.9%) | 8 (11.9%) | 44 (28.4%) | 42 (15.6%) |
| Internal Medicine | 516 | 48.9 | 61 (59.8%) | 50 (51.5%) | 146 (52.5%) | 51 (59.3%) | 35 (52.2%) | 32 (20.6%) | 141 (52.2%) |
### Shift

| Shift                        | Morning | Night/Afternoon shift | Mixed (morning, afternoon, and night shift) |
|------------------------------|---------|-----------------------|--------------------------------------------|
|                              | 209     | 130                   | 716                                        |
|                              | 19.8    | 12.3                  | 67.9                                       |
|                              | 21 (20.6%) | 21 (20.6%)       | 60 (58.8%)                                 |
|                              | 13 (13.4%) | 0 (0%)              | 84 (86.6%)                                 |
|                              | 61 (21.9%) | 36 (12.9%)         | 181 (65.1%)                                |
|                              | 10 (11.6%) | 6 (7.0%)            | 70 (81.4%)                                 |
|                              | 9 (13.4%)  | 18 (26.9%)          | 40 (59.7%)                                 |
|                              | 32 (20.6%) | 9 (5.8%)            | 114 (73.5%)                                |
|                              | 63 (23.3%) | 40 (14.8%)         | 167 (61.9%)                                |

### Years experience in nursing

| Years experience in nursing | 0 to 5 | 6 to 15 | 16 to 25 | 26 to 31 | > 31 |
|-----------------------------|-------|--------|----------|----------|------|
|                             | 114   | 143    | 273      | 272      | 253  |
|                             | 10.8  | 13.6   | 25.9     | 25.8     | 24.0 |
|                             | 16 (15.7%) | 12 (11.8%) | 25 (24.5%) | 22 (21.3%) | 27 (26.7%) |
|                             | 14 (14.4%) | 7 (7.2%)  | 15 (15.5%) | 24 (24.7%) | 37 (38.1%) |
|                             | 25 (9%)  | 33 (11.9%) | 75 (27.0%) | 76 (27.3)  | 69 (24.9%) |
|                             | 0 (0%)   | 3 (3.5%)  | 18 (20.9%) | 31 (36.0%) | 34 (39.5%) |
|                             | 2 (3.0%)  | 4 (6.0%)   | 19 (28.4%) | 26 (38.8%) | 16 (23.9%) |
|                             | 20 (12.9%) | 38 (24.5%) | 50 (32.3%) | 33 (21.3%) | 14 (9.0%)  |
|                             | 37 (13.7%) | 46 (17.0%)  | 71 (26.3%) | 60 (32.2%) | 56 (20.7%) |

### Registered nurses' attitudes to EOL care

According to the study, RNs working in the three different profiles emphasized safe and effective care for patients at the EOL. The RN also emphasized the importance of meeting the patient's spiritual needs in EOL care, i.e., the patient should have the right to a dignified and painless death. The survey revealed a statistically significant difference between RNs in the three departments in attitudes about working with seriously ill patients who frequently died. RNs in the surgical department more than those in the intensive care and internal medicine departments felt these nurses required the help of a psychologist ($M = 4.20, p = .009$). The RNs in the surgical department also indicated stronger attitudes that family and relatives should not be limited in time and duration of the patient visit ($M = 4.16, p < .001$). Meanwhile, nurses working in the internal medicine departments were more likely to say that patients should not be permanently suppressed by sedation drugs ($M = 3.69, p < .001$).
And RNs working in intensive care departments felt most psychologically prepared to deal with the problems at the EOL ($M = 3.67, p = .011$) (Table 2).

### Table 2

| Row No. | Statement                                                                 | Surgical department | Intensive care department | Internal medicine department | \( N = 1055 \) |
|---------|---------------------------------------------------------------------------|---------------------|---------------------------|------------------------------|---------------|
| 1       | The patient should continue to receive all interventions to prevent pressure sores | 4.66 (0.59)         | 4.73 (0.53)               | 4.68 (0.51)                 | 0.331\(^c\)  |
| 2       | The patient is entitled to a dignified and painless death                 | 4.62 (0.60)         | 4.69 (0.54)               | 4.67 (0.56)                 | 0.392\(^c\)  |
| 3       | The patient should always be given the opportunity to receive last rituals that are appropriate to the religious and spiritual beliefs of the patient and their family | 4.60 (0.58)         | 4.62 (0.62)               | 4.60 (0.58)                 | 0.839\(^c\)  |
| 4       | The patient should be cared for in the privacy of a private room          | 4.55 (0.60)         | 4.56 (0.67)               | 4.54 (0.63)                 | 0.659\(^c\)  |
| 5       | During EOL care, oro/endotracheal suction should be continued to maintain the airway of the patient | 4.45 (0.60)         | 4.44 (0.67)               | 4.42 (0.60)                 | 0.629\(^c\)  |
| 6       | Healthcare professionals working with patients with extremely serious conditions and frequent deaths, need psychological help | 4.20 (0.79)         | 4.05 (0.83)               | 4.01 (0.89)                 | 0.009\(^c\)  |
| Page | Statement                                                                                                                                     | Mean (SD) Patient | Mean (SD) Doctor | Mean (SD) Nurse | p-value |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------|-----------------|---------|
| 7    | Patient should be permitted to visit at any time, day or night                                                                                  | 4.16 (1.04)       | 3.28 (1.25)      | 4.04 (1.09)     | <0.001c |
| 8    | It is advisable for a patient suffering from an incurable disease to be given the optimum amount of painkillers, despite the fact that this would accelerate his death. | 4.14 (0.78)       | 4.21 (0.76)      | 4.20 (0.78)     | 0.419c  |
| 9    | Patients have the right to refuse treatment, even though this would result in their death                                                      | 3.87 (0.93)       | 3.86 (0.97)      | 3.95 (0.91)     | 0.354c  |
| 10   | Some patients may be excluded from their treatment and nursing decisions because of doubts about their ability to assess the situation     | 3.86 (0.78)       | 3.92 (0.80)      | 3.83 (0.83)     | 0.481c  |
| 11   | Talking with doctors about solving end-of-life problems in a patient has a positive effect on nurses' job satisfaction.                      | 3.76 (0.94)       | 3.91 (0.86)      | 3.73 (0.98)     | 0.128c  |
| 12   | During EOL care, the patient should continue to receive fluids to maintain hydration                                                          | 3.72 (1.04)       | 3.87 (1.04)      | 3.70 (1.03)     | 0.126c  |
| 13   | Nurses have sufficient knowledge of their patients to make an informed decision about what they want.                                          | 3.67 (0.97)       | 3.62 (0.97)      | 3.71 (1.01)     | 0.393c  |
| 14   | Interviews with the patient's family about solving the patient's end-of-life problems have a positive influence on nurses' job satisfaction | 3.64 (1.00)       | 3.66 (0.95)      | 3.59 (1.01)     | 0.730c  |

Patient consciousness
Registered nurses' attitudes to obstacles and supportive behaviour in providing EOL care

Analyzing the most common obstacles to EOL care, the survey data indicated that for the first block of obstacles, with a comparable average of more than 4 points, the respondents in all departments attributed dealing with angry family members as an obstacle (p = .004) and inadequate understanding by the patient's relatives of the nursing care (NS). RNs working in intensive care departments were more likely to identify a obstacles of family and friends who regularly called the nurse to find out about the patient's condition rather than listening to informed family members (M = 4.02, p = .034). Also for intensive care RNs, family members disagreeing on the kind of care that was most adequate for the patient was perceived as an obstacle (M = 3.90, p = .046).

For the second obstacle block, with a mean score of 4 to 3.5, RNs assigned family members' inadequate knowledge about the situation and lack of time to talk to patients about their wishes for EOL problems as obstacles. And in the third obstacle block, with scores of less than 3.5, the RN attributed the lack of knowledge to communicate with the bereaved patient's family, the lack of evaluation of nurses' opinions, and the evasion of physicians to talk about diagnosis and over-optimistic view of the situation as obstacles (Table 3). Group differences were not statistically significant.

Table 3
RN attitudes to potential barriers in ensuring patient care at end-of-life depending on the department

| Row. No. | Statement | Surgical department N = 344 | Intensive care department N = 195 | Internal medicine department N = 516 | N = 1055 |
|----------|-----------|-----------------------------|-----------------------------------|---------------------------------------|-----------|
|          |           | M/SD                        | M/SD                              | M/SD                                  | p         |
|   | relatives having inadequate understanding of the situation interfere with the nurses’ duties | 4.16 (0.73) | 4.09 (0.75) | 4.18 (0.72) | 0.319<sup>c</sup> |
|---|---------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|-------------|-----------------|
| 2 | Nurses have to deal with angry patient’s family members | 4.04 (0.86) | 4.05 (0.87) | 4.18 (0.87) | 0.004<sup>c</sup> |
| 3 | Family has no access to psychological help after being informed about the patient’s diagnosis | 3.97 (0.91) | 4.04 (0.89) | 3.86 (1.04) | 0.217<sup>c</sup> |
| 4 | Usually there is no time for conversations with patients about their wishes concerning the end of life decisions | 3.95 (0.85) | 3.89 (0.87) | 4.00 (0.87) | 0.150<sup>c</sup> |
| 5 | Family members or friends regularly call for a nurse in order to find out about the patient’s condition instead of addressing an informed family member | 3.83 (0.87) | 4.02 (0.85) | 3.83 (0.92) | 0.034<sup>c</sup> |
| 6 | Very often, the patient’s family members disagree on which treatment is most appropriate | 3.80 (0.81) | 3.75 (0.89) | 3.83 (0.85) | 0.449<sup>c</sup> |
| 7 | The patient’s family members disagree on what kind of care is the most adequate | 3.72 (0.87) | 3.90 (0.78) | 3.85 (0.87) | 0.046<sup>c</sup> |
| 8 | The lack of nursing knowledge on how to treat the patient’s grieving family | 3.42 (0.99) | 3.33 (0.99) | 3.26 (1.06) | 0.125<sup>c</sup> |
| 9 | The nurse’s opinion on immediate patient care is not welcome, valued or discussed | 3.40 (1.09) | 3.46 (1.08) | 3.39 (1.11) | 0.770<sup>c</sup> |

1. Physicians are too
|   | optimistic about the patient’s survival prospects during conversations with the patient’s family members |   |   |   |
|---|--------------------------------------------------------------------------------------------------|---|---|---|
| 10 | 3.27 (0.99)                                                                                     | 3.19 (0.97) | 3.25 (1.03) | 0.627<sup>c</sup> |

|   | Physicians are evasive and avoid conversation with the patient and/or family members |   |   |   |
|---|----------------------------------------------------------------------------------------|---|---|---|
| 11 | 3.09 (1.10)                                                                            | 2.91 (1.07) | 3.08 (1.14) | 0.251<sup>c</sup> |

*Used Kruskal Wallis Test

Data for analyzing factors that would facilitate EOL care are presented in Table 3. RNs across all departments indicated that patient family education on how to deal with the seriously ill would facilitate the work of nurses. Similarly, nurses working in all three departments said that EOL training, volunteering, and family involvement would facilitate EOL care (Table 4). Group differences were not statistically significant.
Table 4
Factors facilitating end-of-life care for patients depending on the department

| Row. No. | Statement                                                                 | Surgical department N = 344 | Intensive care department N = 195 | Internal medicine department N = 516 | N = 1055 |
|----------|---------------------------------------------------------------------------|-----------------------------|-----------------------------------|--------------------------------------|----------|
|          |                                                                           | M/SD                        | M/SD                              | MSD                                  | p        |
| 1        | Teaching families how to act with a dying patient                         | 4.08 (0.79 )                | 4.15 (0.65)                       | 4.18 (0.67)                          | 0.343ᶜ   |
| 2        | End of life patient care training                                         | 3.97 (0.80 )                | 3.97 (0.67)                       | 4.06 (0.75)                          | 0.066ᶜ   |
| 3        | Auxiliary personnel helping the nurse with the patient’s care             | 3.74 (0.86)                 | 3.66 (0.90)                       | 3.80 (0.93)                          | 0.130ᶜ   |
| 4        | Having one family member be the designated contact person for all other family members regarding information about the patient. | 3.66 (1.05)                 | 3.87 (0.92)                       | 3.75 (1.03)                          | 0.131ᶜ   |
| 5        | The family of the patient who appreciates your work in caring for a patient with a serious condition | 3.61 (0.91)                 | 3.58 (0.86)                       | 3.55 (0.99)                          | 0.736ᶜ   |
| 6        | Nurse talking with patient about their feelings and thoughts about death | 3.47 (0.93)                 | 3.60 (0.88 )                      | 3.49 (0.97)                          | 0.263ᶜ   |

* Used Kruskal Wallis Test

Discussion

The quality of care for dying patients is determined by the nurses’ attitude towards the end of life. The RNs who participated in our study stated that it was very important to meet the patient’s spiritual needs. This is also highlighted by research data from other researchers (21, 22). Researchers found that patients in the terminal stages faced not only physical but also spiritual difficulties; they wanted to deal with their spiritual concerns with nurses or other health care staff (23;24). A holistic approach to terminal patient care is essential for EOL care, and spirituality in nursing is an important element of holistic care. Most EOL interventions focus predominantly on symptom control, rather than holistic care (23). This study revealed that nurses had a holistic approach to EOL patient care. They emphasized the importance not only of safe and effective care but also that the patient
should have the right to a dignified and painless death and the last religious ritual should be provided.

Exploring supportive behaviors towards EOL care from the perspective of nurses may lead to better understanding obstacles of EOL care. Several studies have revealed that the main obstacles to EOL care were patients' relatives, who were inadequately judgmental or angry, and physician behavior (18, 25, 26). In this study, RNs in all wards also identified patients' relatives, communication with relatives, and relatives' reluctance to accept poor prognosis as major obstacles to care. A second set of factors attributed by the nurses in this study that made EOL care difficult was lack of time to talk with patients about their preferences for EOL care.

Clinical factors, taking into account the patient's values, should be considered when continuing aggressive care, continuing therapy, or discontinuing life supportive measures. These solutions are complex and differ widely across cultures (9, 10). Doctors play a key role in decisions to start, continue, or stop care. And one of the important obstacles for nurses was that their views on direct patient care were unwanted, undervalued, or irrelevant. One older research study suggested that physicians in Northern and Central Europe were more likely to discuss EOL care with intensive care unit nurses than physicians in the rest of Europe, North America, Japan, or Brazil (27). Diverging attitudes of nurses and physicians towards EOL care can be a serious barrier to quality care (16). But have attitudes changed since then?

Analyzing what behaviors would support and improve EOL care, RNs in this study identified that patient family education on how to treat a seriously ill patient, as well as volunteers to help nurses and evaluate the work of the nurse, would greatly facilitate and improve care. End-of-life care would be facilitated by sufficient time for family members to say goodbye to the deceased, assistance from social workers or volunteers in providing care, having family members accept that patients are dying, and time to spend on emotions (28, 29).

**Conclusion**

Nurses' attitudes towards dying EOL patient care might depend on the departments where they work in clinical counseling. Addressing spiritual needs was identified by nurses as the primary need of patients at the end of life. Obstacles in EOL care, as perceived by RNs, still exist. Family-related obstacles remain one of the main obstacles to EOL care. Also, the behavior of physicians and their relationships with nurses remain one of the most sensitive issues in EOL care. Based on the current identified obstacles, recommendations for possible areas of focus might include: 1) family education and inclusion in EOL care; 2) collaboration between physicians and nurses in EOL decisions for patients; and 3) creating an appropriate work environment that relieves the psychological burden for both family members and carers.

**Relevance to clinical practice**

The results of this study draw attention to family education and inclusion in EOL care; the collaboration between physicians and nurses at the end of life decisions for patients; and creating an appropriate work environment that relieves the psychological burden of both relatives and carers should be implemented in clinical practice and may ensure the quality and safety of care for patients.

**Abbreviations**

EOL

end of life care

**Declarations**

Ethics approval and consent to participate
The study was approved by the Bioethics Committee at the Lithuanian University of Health Sciences. Hospital administrations were informed of the research goals. Verbal informed consent was obtained from each participant following an explanation of the research study goals during the face-to-face recruitment process. Nurses had the right to refuse participation in the study without penalty. The confidentiality of the respondent was assured and anonymity was maintained. All data were summarized and reported only in the aggregate.

**Conent for publication**

Not applicable

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

Study design: A.B., L.L. and J.A.N. Data collection: L.L. Data analysis: A.B and L.L. Manuscript writing and revisions for important intellectual content: A.B., L.L. and J.A.N. All authors read and approved the final manuscript.

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