Healthcare Associated Infections Management inside Intensive Care Units: "What do nurses think about their head nurses?" A qualitative pilot study

Citation: Cappelli E, Fiorini J., Canzan F., Livigni L., Carnevale A., Sili A. "Healthcare Associated Infections Management inside Intensive Care Units: "What do nurses think about their head nurses?" A qualitative pilot study" (2024) infermieristica journal 3(4): 231-238. DOI: 10.36253/if-2923

Received: August 27, 2024 Revised: November 11, 2024

Just accepted online: November 20,

Published: December 31, 2024

Copyright: Cappelli E, Fiorini J., Canzan F., Livigni L., Carnevale A., Sili A. This is an open access, peer-reviewed article published by infermieristica Editore & Firenze University Press (http://www.fupress. com/) and distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files. This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record

Competing Interests: The Author(s) declare(s) no conflict of interest.

Eva Cappelli¹, Jacopo Fiorini², Federica Canzan³, Lucilla Livigni⁴, Angelica Carnevale⁵, Alessandro Sili²

- ¹ Department of Biomedicine and Prevention, University of Tor Vergata, Rome, Italy
- ² Department of Nursing Professions, University Hospital of Tor Vergata, Rome, Italy
- ³ Department of Diagnostics and Public Health, University of Verona, Verona, Italy
- ⁴ Occupational Health Service, University of Rome Tor Vergata, Rome,
- ⁵ Tor Vergata University Hospital, Rome, Italy

Abstract

Introduction. Preventing and controlling Associated Infections (HAIs) caused by Multi Drug Resistant Organisms (MDROs) is one of the primary goals in high-risk settings like Intensive Care Units (ICUs).

The leadership style of the head nurse can result in a reduction of infection rates, such as bloodstream and urinary tract infections; however, it is unclear how leadership can encourage nurses to adhere to Infection Prevention Control (IPC) programs. This study aims to explore the role of the head nurse in encouraging the clinical care team to adhere to IPC practices for preventing and controlling MDRO infections in the ICU.

Methods. single-centre In 2024, interpretative phenomenological study was conducted following the Consolidated Criteria for Reporting Qualitative (COREQ). Nurses and head nurses from three ICUs were recruited. Data were collected through semi-structured interviews and analysed thematically.

Results. Eleven nurses and two head nurses were recruited. The results identified four themes that facilitate the management of HAIs by MDROs: a) awareness of the infection problem, b) head nurse supervision, c) information sharing, and d) distribution of responsibilities. The involvement of leadership and learning through feedback from head nurses are perceived not as barriers but as added value that promotes

the dissemination of best practices.

Conclusions. Recognising the role of the head nurse in the management of HAIs by MDRO would represent an important driver for change in high-risk infection settings. It would enable healthcare organisations to intervene not only with nurses directly involved in patient care but also with middle managers who implement the hospital's directives and produce nursing sensitive outcomes.

Keywords: Infection Prevention and Control, Antimicrobial Resistance, Coordinator, Nurse, Health Behaviour, Critical Care

Introduction

Preventing Healthcare Associated Infections (HAIs) caused by MultiDrug Resistant Organisms (MDROs), such as Escherichia coli resistant to carbapenems, Klebsiella pneumoniae resistant third-generation cephalosporins carbapenems, Enterococcus faecium resistant to vancomycin, Acinetobacter and Pseudomonas aeruginosa resistant to carbapenems, is one of the priorities for patient safety and healthcare systems1.

MDROs responsible for HAIs have a negative impact on the morbidity and mortality rates of hospitalised patients2 because they cause Catheter Associated Urinary Tract Infections (CAUTI), Central Line Associated Bloodstream Infections (CLABSI), and Ventilator Associated Pneumonias (VAP). In some care settings, such as ICU, these phenomena are amplified due to the clinical conditions of the patient and the type of treatments they require³, as well as the risk of transmission by healthcare professionals⁴. A recent European prevalence study on infection risk⁵, found that 78% of patients admitted to intensive care contracted a CLABSI or VAP with multidrug resistance, of which about one-third died due to the infection, and only 10% were discharged alive 28 days after admission.

Although evidence-based best practices to prevent MDRO transmission are well known, their implementation is not always feasible due to numerous contextual variables 3,6. These variables include those related to hospital organisation⁷ and care models⁸, the knowledge and risk perception of healthcare and medical staff⁹, and lastly, the clinical conditions of the patient¹⁰. Therefore, the management of critically ill patients in the ICU requires considerable effort and, above all, a team that is aware, oriented and strongly motivated to pursue the well-being of patients and their caregivers and, consequently, the quality of care^{11.}

In an organizational context, the leadership of the head nurse plays a crucial role, as their ability to influence, inspire, and motivate nurses, primarily through example and ethical guidance in nursing work and adherence to best practices, has a significant impact¹². Numerous studies demonstrate that having an authentic and transformational leader within multidisciplinary team^{13,14} can promote clear transparent communication¹⁵, improve patient satisfaction¹⁶, increase job engagement¹⁵, strengthen commitment⁷, improve performance¹⁷, quality of care¹⁸, and reduce both adverse patient safety events¹⁹, rates of staff turnover¹⁵ and job stress⁷.

Head nurses who can master leadership skills and manage their nursing teams can promote the overall development of professionals and contribute to the adoption of best practices for preventing nosocomial infections, reducing CAUTI and CLABSI rates²⁰, improving nursing sensitive outcomes²¹, and consequently, reducing patient mortality^{22,23}. Although the relationship between the head nurse's leadership style and infection rates in ICU is well known, it is still unclear how it promotes the nursing teams' adherence to Infection Prevention Control (IPC) programs in managing MDROs²⁴. To fill this gap, a qualitative study was conducted to explore how the head nurse's role can encourage adherence to IPC best practices in preventing and controlling MDRO infections in ICU. Understanding, with an interpretative approach, how a head nurse's actions can modulate the work activities of a group of nurses within the ICU would provide healthcare and head nurses with an additional way of intervening and managing HAIs by MDROs and combatting one of the major challenges in this care setting.

Methods

Study Design

An interpretative phenomenological qualitative study²⁵ (IPA) was conducted within three ICUs of an Italian University Hospital (cardiac surgery, post-surgical, and emergency units), where an IPC program is active. This design was utilised for its ability to understand the participants' lived experience ²⁶ in its complexity, providing a detailed and relevant account of the choices and behaviours adopted during nursing practice. To improve the quality of the research process, the principles of the Consolidated Criteria for Reporting Qualitative Research²⁷ (COREQ) were followed (Supplement 1).

Sample

The sample was a convenience sample. To ensure participant heterogeneity the following inclusion criteria were applied: nurses with more than five years of work experience in the emergency care area and at least six months in the ICU and head nurses with at least three years of experience in intensive care. Participation in the study was voluntary. Before enrolment, each participant was informed about the purpose of the study, their privacy was guaranteed, and informed consent was obtained. Participants were enrolled until data saturation²⁸.

Data Collection

A semi-structured interview was created and validated by a professional specialising in advanced nurse training on infection risk and another professional focused on nursing leadership in healthcare. The questions were structured according to the themes present in the international guidelines³ and the study protocol²⁴. Additionally, each participant was asked about their gender, age, type of education, years of professional experience, and the ward they worked in (Supplement 2a,b). The interviews were conducted individually, audiorecorded, and conducted within a safe space free of potential influences on the participants (e.g., away from the ward, low noise levels). The interviews were conducted by two researchers experienced in qualitative research and occupational psychology (EC, LL), who did not work for the hospital where the data was collected. Furthermore, a logbook was used to collect non-verbal expressions, which were integrated into the verbal data during the decoding and analysis phases. The average duration of an interview was approximately 30 minutes.

Data Analysis

Each interview was transcribed and enriched with non-verbal subtleties recorded in the logbook to characterise the management practices conveyed by the head nurse in handling MDRO infections and implemented by nurses in their care practices. The transcription, coding, and analysis were conducted following the approach of Smith²⁵ and Giorgi²⁶. The process of data interpretation began with the first interview and extended through the analysis of all transcriptions. The interviews were numbered and categorised by the following professional categories (Nurse N° 1, N1; Head Nurse N° 1, HN1).

The transcriptions were read several times to obtain an overview of the information ²⁸. In the first phase of analysis, initial codes were generated by coding the main characteristics of the studied phenomenon and reporting them in the margin of each text²⁹. Subsequently, the identified codes were grouped into potential themes, defined with clear and simple statements. Finally, the themes were connected to generate a map.

Socio-demographic characteristics were analysed using descriptive analysis, with absolute and percentage frequencies.

Methodical Rigor

To ensure rigor and reliability, the researchers who developed and asked the interview questions were experts in qualitative research, nursing work organisation, infection risk and occupational psychology (EC, LL, JF). The researchers independently conducted the entire data collection process, and the codes only emerged after the results were shared. Confirmability and consistency of the analysis were ensured through preliminary meetings to discuss the findings. Codes and themes were discussed with the entire research group until approval was reached by all members²⁹. Reliability was ensured by providing a detailed description of the data and including contextually relevant quotes from participants within tables to vividly illustrate each individual's perspective.

Ethical Considerations

The research was conducted following the principles of the Declaration of Helsinki³⁰. The Ethics Committee of the University Hospital where the data collection took place approved the study under protocol number (Prot. N° RS 104.23). Participants were first informed about the study's purpose and subsequently signed

an informed consent form. Anonymity was guaranteed, and the transcripts included in the text were not traceable to any individual or their specific context. Participants were free to decline to answer any questions that might cause discomfort and could withdraw from the study at any time.

Results

Sample Characteristics

In compliance with the inclusion criteria, data saturation occurred with 11 nurses and 2 head nurses. The 13 participants interviewed were aged between 35 and 52 years, 9 were women, and 54% held a Master of Science Degree in Nursing (Table 1). The participants had been working as nurses for at least 10 years and in intensive care for 4 years.

Data analysis revealed that the main themes promoting the management of HAIs caused by MDROs are associated with four main leadership practices: a) awareness of the infection problem, b) head nurse supervision, c) information sharing, d) distribution of responsibilities.

The results and qualitative interview data are presented and grouped based on the themes identified during the analysis process (Figure 1).

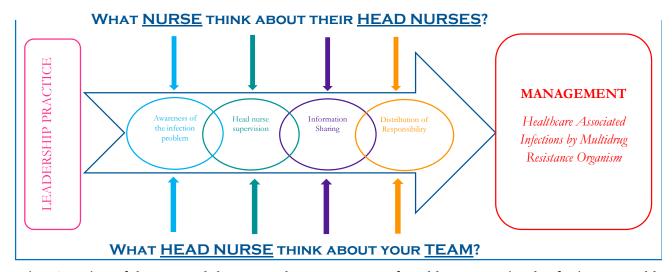


Fig.1 Overview of the emerged themes on the management of Healthcare Associated Infections caused by MultiDrug-Resistant Organisms

Awareness of the infection problem

The head nurse and nurses interviewed provided their perspectives on managing HAIs caused by MDROs, offering various reflections on this practice.

Some interviewees reported that the problem of infections within their ward is "meticulously" (N1) attended to, because critically ill patients are "highly susceptible to infectious complications" (N3), which can sometimes lead to the patient's "death"

After the COVID-19 pandemic, there has been a "change in direction" (HN1) in the hospital, firstly on the part of healthcare managers and subsequently also by the "entire care team" (HN1). Even infectious disease specialists "were no longer regarded as troublesome consultants" (HN1). This meticulous attention is perceived by many interviewees as a "continuous incentive to analyse and correct the behaviour of all professionals involved in the patient care process" (N6).

Head Nurse Supervision

The control and management exercised by the head nurse within their ward and over the nursing staff and cleaning staff can enable them to motivate adherence to best clinical practices. Supervision can be carried out through directive or motherly feedback, with the ultimate goal of "helping to understand the rationale behind everything that is said and then done" (N4). In both cases, the head nurse demonstrates a significant sensitivity to infection problems, and actively promotes and supports various infection control training initiatives that the hospital, and in particular the Hospital Infection Committee, makes available to everyone. In this regard, nurses reported that their head nurse is "present, attentive to infections, and supportive" (N5). This leads to a certain sensitivity to the results and quality of care, and, at the same time, provides an opportunity to re-educate nurses on best practices. Indeed, the interviews revealed that head nurses encourage their nurses to "participate in hospital courses on hand hygiene and similar training" (N5).

Feedback from the head nurse helped nurses identify priorities and implement necessary process changes to address infection problems. For instance, during a night shift, upon the arrival of a patient with a "New Delhi" infection, nurses self-managed, redistributed their workloads and implemented staff cohorts, where "only one nurse was dedicated to the care of the infected patient" (HN2).

Information Sharing

To support decision-making in patient care practices and to optimise available resources, nurses have identified information sharing as crucial. The primary methods used by the head nurse to communicate information — clinical and administrative — include emails, daily briefings, informal and formal meetings such as audits, and signage.

The most common communication mode is via email, through which "new hospital procedures, new ministerial circulars, and new protocols" (N8) are usually disseminated. Infection data and objectives are discussed during internal audits. However, "true information sharing occurs during coffee breaks" (N3) and morning briefings. During coffee breaks, "the coordinator calmly explains and clarifies what needs to be done" (N3). Instead, a briefing is a formal meeting for sharing and making clinical care decisions, where doctors and nurses discuss each patient to establish medium- and long-term care plans. Nurses emphasised the importance of attending these meetings as they facilitate "the updating of the clinical conditions of all patients in the ward" (N4).

Additionally, ward signage is used, such as coloured tags placed at the head of patients' beds indicating the type of isolation required for pathogen colonisation/infection, or posters on proper hand hygiene³¹ and the donning/doffing of personal protective equipment³². While participants recognise their usefulness, they feel that the signage is not "very visible to the staff, external consultants, and even the patients' relatives themselves" (N3). Many suggested that an optimal strategy should be identified so that the signage can catch the attention of those approaching the inpatient unit of the isolated patient.

Distribution of Responsibilities

For infection management of MDROs to become a priority throughout the hospital, each

member of the care process must recognise their responsibilities and errors in their choices and actions. Nurses stated that the head nurse is responsible for creating an efficient and effective work environment, which includes delegating certain tasks and actively involving doctors and external consultants in infection prevention processes. In practice, within the team, the head nurse is one who "guides the behaviour of less compliant individuals" (N3) by proposing "targeted updates" (N3) and "empowering some nurses" (N6) on specific IPC activities, such as environmental sanitation.

It is necessary for professionals who do not regularly work in intensive settings but visit for consultations to recognise infection sources and approach safely by "wearing gowns and washing hands before and after approaching the patient" (HN2). Interviewees emphasised the need for an open organisational climate within the team, where problems are discussed transparently, avoiding institutional hierarchies. Indeed, all involved, including residents, need to "be aware of the presence of infections and how to behave" (N3) and everyone must "give due value even to aspects that are not always relevant to their professional profile" (N6). Even leaders are responsible for infection management, and, according to the experts, their "presence, control, and decisions" (HN2) could be crucial in collaboratively solving some of the problems in the operational context.

Discussion

This study aimed to explore how the role of the head nurse can support nurses in preventing and controlling MDRO infections in intensive care settings. The results indicate that a head nurse who attends to the problem, supervises, shares information, and distributes responsibilities can significantly enhance nurses' adherence to MDRO infection prevention and management in an ICU.

Although the power of the clinical care team is crucial in preventing infections, it is undeniable that the governance of healthcare leaders and the ethical choices of the hospital can influence the hospital culture³³. Indeed, as described by both nurses and head nurses, having an authentic and transformational head nurse alone is not sufficient; it is also necessary to actively involve managers in these processes. This ensures that actions and directives align with common and shared goals. Managers must provide head nurses and nurses with adequate training and a certain

level of operational flexibility so that teams are performing well and adequately prepared to change new national and internal political and epidemiological choices and strategies^{34.}

Participative, collaborative, and contextspecific head nurse leadership can positively impact the well-being of nursing staff and, consequently, affect MDRO infections²⁴. However, this influence alone is not always sufficient to support all infection prevention practices. Nurses need to perceive their leaders as committed, determined, and engaged to effectively channel their efforts^{7,12}. The way the head nurse provides feedback to frontline staff is not binding for the implementation of good practice. Providing feedback to frontline staff does not necessarily ensure the implementation of good practices. Having leaders with a direct or motherly communication approach is not perceived as a hindering factor, but as an added value that favours the dissemination of best practices. Furthermore, recognising the importance of an effective leadership style enables all team members to share goals, responsibilities, and outcomes¹⁵.

Periodic updates via email or routine scheduled meetings can assist head nurse even when they are not physically present in the hospital. Previous research has shown that formal and informal communication, as well as interactions with the head nurse and other team members, can provide significant opportunities for nurses and clinicians to address knowledge gaps and improve care practices²³. Additionally, the use of operational tools and systems, such as head nurse feedback, audits, hospital procedures, and continuous training, allows all professionals to be more accountable and autonomous, and to participate more actively in patient care, reducing MDRO infections^{24,18,14}.

Another aspect that emerged from the results was the distribution of responsibilities and their strategic role in infection management. Sometimes, interviewees identified difficulties in adherence to best IPC practices by doctors, particularly residents, who often do not receive adequate training during their educational programs³⁵. In conclusion, it is crucial that each professional independently and responsibly recognises the infection problem, communicates doubts and concerns with the rest of the team, shares best strategies, and implements them to control and manage infections effectively3.

Limitations of the Study

The results of this study should be considered in light of certain limitations. The study sample, limited to nurses and head nurses from a single hospital, may not accurately reflect the diversity and complexity of the phenomenon studied. To gain a more comprehensive understanding, it is important to explore the perspectives of other healthcare professionals, such as doctors, residents, cleaning staff, and support personnel. Therefore, further research is needed that includes participants from different operational settings as well as other professionals, such as medical doctors, infection risk specialists, physiotherapists, and technicians. This will help achieve a more complete understanding of the issues discussed and examine how various leadership practices could be more effective in preventing HAI by MDROs.

Conclusions

Having a head nurse who can effectively supervise, engage, share information, and provide feedback to frontline staff facilitates the prevention and management of HAIs by MDROs. The role that the head nurse plays in multidisciplinary teams is crucial for maintaining adherence to best clinical practices, positively reinforcing key concepts that ensure good work performance and quality nursing care for users. For nurses, being guided by a leader with these characteristics means being encouraged to participate in advanced training, to refine their skills and competencies, and to contribute directly to the improvement of nursing sensitive outcomes.

Implications for Clinical Practice

Healthcare organisations have an urgent need to address problems related to MDRO Implementing infections. strategies enhance the leadership of the head nurse can be successful in promoting efficient and, at the same time, sustainable solutions. Sharing data and information, proactively involving all stakeholders in the care process, breaking down institutional hierarchies, adopting shared responsibilities, and fostering a healthcare culture focused on safety can help reduce this healthcare burden.

© The Author(s), under esclusive licence to infermieristica Editore Limited 2024.

References

- WHO. World Health Organization. Global report on infection prevention and control. 2022. Accessed August 01, 2024. http://apps.who.int/bookorders.
- Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19:56-66.
- ECDC. European Centre for Disease Prevention and Control and World Health Organization Antimicrobial resistance surveillance in Europe 2023 - 2021, 2023, Accessed August 01, 2024, https://www.ecdc.europa.eu/ sites/default/files/documents/Antimicrobial%20resistance%20surveillance%20in%20Europe%202023%20 -%202021%20data.pdf.
- 4. de Kraker MEA, Lipsitch M. Burden of Antimicrobial Resistance: Compared to What?. Epidemiol Rev. 2022;
- Tabah A, Buetti N, Staiquly Q, et al. Epidemiology and outcomes of hospital-acquired bloodstream infections in intensive care unit patients: the EUROBACT-2 international cohort study. Intensive Care Med. 2023; 49:178-
- Allegranzi B, Bischoff P, de Jonge S, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016; 16:e276-e287.
- Cummings GG, MacGregor T, Davey M, et al. Leadership styles and outcome patterns for the nursing workforce and work environment: a systematic review. Int J Nurs Stud. 2018; 47:363-385.
- Mitchell BG, Gardner A, Stone PW, Hall L, Pogorzelska-Maziarz M. Hospital Staffing and Health Care-Associated Infections: A Systematic Review of the Literature. Jt Comm J Qual Patient Saf. 2018; 44:613-622.
- Alhumaid S, Al Mutair A, Al Alawi Z, et al. Knowledge of infection prevention and control among healthcare workers and factors influencing compliance: a systematic review. Antimicrob Resist Infect Control. 2021; 10:86. Published 2021 Jun 3.
- 10. Haque M, McKimm J, Sartelli M, et al. Strategies to Prevent Healthcare-Associated Infections: A Narrative Overview. Risk Manag Healthc Policy. 2020; 13:1765-1780. Published 2020 Sep 28.
- 11. Alloubani A, Akhu-Zaheya L, Abdelhafiz IM, Almatari M. Leadership styles' influence on the quality of nursing care. Int J Health Care Qual Assur. 2019; 32:1022-1033.
- 12. Ferreira TDM, de Mesquita GR, de Melo GC, et al. The influence of nursing leadership styles on the outcomes of patients, professionals and institutions: An integrative review. J Nurs Manag. 2022; 30:936-953.
- 13. Avolio BJ, Walumbwa FO, Weber TJ. Leadership: current theories, research, and future directions. Annu Rev Psychol. 2009; 60:421-449.
- 14. Boamah SA, Spence Laschinger HK, Wong C, Clarke S. Effect of transformational leadership on job satisfaction and patient safety outcomes. Nurs Outlook. 2018; 66:180-189.
- 15. Cziraki K, Wong C, Kerr M, Finegan J. Leader empowering behaviour: relationships with nurse and patient outcomes. Leadersh Health Serv (Bradf Engl). 2020; 33:397-415.
- 16. Zaghini F, Biagioli V, Proietti M, Badolamenti S, Fiorini J, Sili A. The role of occupational stress in the association between emotional labor and burnout in nurses: A cross-sectional study. Appl Nurs Res. 2020; 54:151277.
- 17. Landerfelt PE, Lewis A, Li Y, Cimiotti JP. Nursing leadership and the reduction of catheter-associated urinary tract infection. Am J Infect Control. 2020; 48:1546-1548.
- 18. Asif M, Jameel A, Hussain A, Hwang J, Sahito N. Linking Transformational Leadership with Nurse-Assessed Adverse Patient Outcomes and the Quality of Care: Assessing the Role of Job Satisfaction and Structural Empowerment. Int J Environ Res Public Health. 2019; 16:2381. Published 2019 Jul 4.
- 19. Wong CA, Cummings GG, Ducharme L. The relationship between nursing leadership and patient outcomes: a systematic review update. J Nurs Manag. 2013; 21:709-724.
- 20. Cappelli E, Zaghini F, Fiorini J, Sili A. Healthcare-associated infections and nursing leadership: A systematic review. Journal of Infection Prevention. 2024; 0.
- 21. Fiorini J, Zaghini F, Mannocci A, Sili A. Nursing leadership in clinical practice, its efficacy and repercussion on nursing-sensitive outcomes: A cross-sectional multicentre protocol study. J Nurs Manag. 2022; 30:3178-
- 22. Hegarty J, Murphy S, Creedon S, Wills T, Savage E, Barry F, Smiddy M, Coffey A, Burton A, O'Brien D, Horgan S, Nibhuachalla C, Brennan C, Agreli H & Drennan J. Leadership perspective on the implementation of guidelines on healthcare-associated infections. BMJ Leader. 2019; 3:43-51.
- 23. van Buijtene A, Foster D. Does a hospital culture influence adherence to infection prevention and control and rates of healthcare associated infection? A literature review. J Infect Prev. 2019; 20:5-17.
- 24. Cappelli E, Fiorini J, Zaghini F, Canzan F, Sili A. Head Nurse Leadership: Facilitators and Barriers to Adherence to Infection Prevention and Control Programs-A Qualitative Study Protocol. Nurs Rep. 2024; 14:1849-1858. Published 2024 Jul 26.
- 25. Smith J, Flowers PA & Larkin M. Interpretative Phenomenological Analysis. Theory, Method and Research.

- Qualitative Research in Psychology. 2009; 6:346-347.
- 26. Giorgi A. The descriptive phenomenological method in psychology: A modified Husserlian approach. Pittsburgh, PA: Duquesne University Press. Journal of Phenomenological Psychology. 2009; 41:269-276.
- 27. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007; 19:349-357.
- 28. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. Nurs Health Sci. 2013; 15:398-405.