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Testing a family supportive end of life care intervention in a Chinese neonatal intensive care unit: A quasi-experimental study with a non-randomized controlled trial design

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Author contribution statement

Concept and design: Zhu Li-hui, Zhang Rong, Peng xiao-ming and Xiong yue-e, Jos M. Latour. Data collection: Chen Mu-hua, Zhang Na, Tang qian, Chen ke-liang, Zhang Rong. Statistical analysis: Tang qian, Zhang Na, Zhang Rong. Drafting of the manuscript: Zhang Rong and Jos M Latour. Providing revisions of the manuscript for important intellectual content: Zhu Li-hui, Peng xiao-ming and Xiong yue-e, Zhang Na and Tang qian. All authors contributed to the article and approved the submitted version.

Keywords

Neonatal death, End-of-life care, infants, Parents, neonatal intensive care unit, family-centered care

Abstract

Background: Neonatal death often occurs in tertiary Neonatal Intensive Care Units (NICUs). In China, end-of-life-care (EOLC) does not always involve parents.

Aim: The aim of this study is to evaluate a parent support intervention to integrate parents at the end of life of their infant in the NICU.

Methods: A quasi-experimental study using a non-randomized clinical trial design was conducted between May 2020 and September 2021. Participants were infants in an EOLC pathway in the NICU and their parents. Parents were allocated into a family supportive EOLC intervention group or a standard EOLC group based on their wishes. Primary outcomes were depression (Edinburgh Postnatal Depression Scale for mothers; Hamilton Depression rating scale for fathers) and satisfaction. Student t-test for continuous variables and the Chi-square test categorical variables were used in the statistical analysis.

Results: In the study period, 62 infants died and 45 infants and 90 parents were enrolled; intervention group 20 infants, standard EOLC group 25 infants. The most common causes of death in both groups were congenital abnormalities ($n=20$, 44%). Mean gestational age of infants between the family supportive EOLC group and standard EOLC group was 31.45 versus 33.8 weeks ($p=0.234$). Parents between both groups did not differ in terms of age, delivery of infant, and economic status. In the family support group, higher education levels were observed among mother ($p=0.026$) and fathers ($p=0.020$). Both mothers and fathers in the family supportive EOLC group had less depression compared to the standard EOLC groups; mothers (mean 6.90 vs 7.56; $p=0.017$) and fathers (mean 20.7 vs 23.1; $p<0.001$). Parents reported higher satisfaction in the family supportive EOLC group (mean 88.9 vs 86.6; $p<0.001$).

Conclusions: Supporting parents in their EOLC pathway in Chinese NICUs might decreased their depression after the death of their infant and increase satisfaction. Further research need to focus on long-term effects and expand on larger populations with different cultural backgrounds.

Contribution to the field

In China, neonatal death on 2019 was 3.5 per 1000 live births, which counts around 57,000 deaths. In mainland China, parents are mostly the main decision-makers in withdrawing life-sustaining treatments in infants and neonatologists often follow the wishes of the parents. However, there is limited experience in supporting parents after the decision is made to withdraw treatment. The aim of this study was to develop and test a family supportive end-of-life care intervention to decrease parental depression and increase parent satisfaction. Our study indicated that providing a comfortable environment and supportive care to parents during the final days of life of an infant decrease their depression and increases parent satisfaction. The NICUs in mainland China and beyond might consider involving parents in end-of-life care by providing a single room, have a dedicated psychologist available and provide supportive commemoration materials.

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Studies involving animal subjects

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Studies involving human subjects

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1 **Testing a family supportive end of life care intervention in a Chinese neonatal**
2 **intensive care unit: A quasi-experimental study with a non-randomized**
3 **controlled trial design**

4 **Running Title: End-of-life care in NICU**

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24 **Key words:** Neonatal death, End-of-life care, Infants, Parents, Neonatal Intensive
25 Care Unit, Family-Centered Care.

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30 **ABSTRACT**

31 **Background:** Neonatal death often occurs in tertiary Neonatal Intensive Care Units
32 (NICUs). In China, end-of-life-care (EOLC) does not always involve parents.

33 **Aim:** The aim of this study is to evaluate a parent support intervention to integrate
34 parents at the end of life of their infant in the NICU.

35 **Methods:** A quasi-experimental study using a non-randomized clinical trial design
36 was conducted between May 2020 and September 2021. Participants were infants in
37 an EOLC pathway in the NICU and their parents. Parents were allocated into a family
38 supportive EOLC intervention group or a standard EOLC group based on their wishes.
39 The primary outcomes depression (Edinburgh Postnatal Depression Scale for mothers;
40 Hamilton Depression rating scale for fathers) and Satisfaction with Care were
41 measured one week after infants' death. Student t-test for continuous variables and the
42 Chi-square test categorical variables were used in the statistical analysis.

43 **Results:** In the study period, 62 infants died and 45 infants and 90 parents were
44 enrolled; intervention group 20 infants, standard EOLC group 25 infants. The most
45 common causes of death in both groups were congenital abnormalities (n=20, 44%).
46 Mean gestational age of infants between the family supportive EOLC group and
47 standard EOLC group was 31.45 versus 33.8 weeks (p=0.234). Parents between both
48 groups did not differ in terms of age, delivery of infant, and economic status. In the
49 family support group, higher education levels were observed among mother (p=0.026)
50 and fathers (p=0.020). Both mothers and fathers in the family supportive EOLC group
51 had less depression compared to the standard EOLC groups; mothers (mean 6.90 vs
52 7.56; p=0.017) and fathers (mean 20.7 vs 23.1; p<0.001). Parents reported higher
53 satisfaction in the family supportive EOLC group (mean 88.9 vs 86.6; p<0.001).

54 **Conclusions:** Supporting parents in EOLC in Chinese NICUs might decreased their
55 depression and increase satisfaction after the death of their infant. Future research
56 needs to focus on long-term effects and expand on larger populations with different
57 cultural backgrounds.

71

72 **Key words:** Neonatal death, End-of-life care, Infants, Parents, Neonatal Intensive
73 Care Unit, Family-Centered Care.

74 **INTRODUCTION**

75 In 2019, the World Health Organization (WHO) reported that neonatal death within
76 the first 28 days of life reached 17 per 1000 live births, estimating around 2.4 million
77 neonates (1). In China, neonatal death was 3.5 per 1000 live births in 2019, which was
78 around 57,000 deaths (2). End-of-life care (EOLC) has been emphasized by the WHO
79 Global Action Plan 2013-2020 (3,4). The mandate by the WHO highlights the need
80 for improvement in infant’s EOLC and the support of parents and family in the
81 Neonatal Intensive Care Unit (NICU).

82 From a historical perspective, the care around death of neonates was first
83 addressed in the United States in the 1980s. In 1982, Silverman described that EOLC
84 has been successfully implemented in hospice settings for newborns (5). Over the
85 years, EOLC has been further progressed in European countries and Northern
86 America leading to a number of national guidelines and clinical practice
87 recommendations (6-8). And recently, palliative care has become a new service in
88 many healthcare settings and EOLC can play an important part in palliative care.

89 Recent studies have focused on EOLC decisions (9), pain and comfort
90 management (10) and implementation of the palliative care sub-specialty within
91 Neonatology (11). Unfortunately, EOLC received less attention in Asia, specifically in
92 mainland China (12). A literature review investigating the EOLC practices in Asian
93 countries identified only 11 empirical studies from Hong Kong, India, Israel, Japan,
94 Mongolia, Taiwan, and Turkey (13). Studies around EOLC from Taiwan explored the
95 attitudes of NICU staff and identified a number of barriers in delivering high quality
96 of EOLC (14,15). The most common barriers were insufficient training in
97 communication with parents, staffing shortages and lack of unit policies in supporting
98 palliative care. Compared to European countries and United States, less evidence is
99 available from Asian countries in how parents are involved in the care of their infant
100 and specifically how family-centered care (FCC) is included in EOLC.

101 Since 2010, FCC has gained more attention in China and has been gradually
102 implemented in Chinese NICUs. An FCC program was implemented in our NICU
103 department at Hunan Children’s Hospital in Changsha, China, and contributed to a
104 wider implementation across Chinese NICUs (16-19). Three trials were conducted to
105 test FCC interventions related to parental empowerment (training of parents and
106 participation of parents in the care of their infant) demonstrating significant
107 improvements in breastfeeding and quality of life. The studies also documented a
108 decrease in parental anxiety and depression as well as an improvement in parent
109 satisfaction (16-18). Despite different beliefs, cultures, attitudes and policy, the EOLC
110 remains unexplored in China without rigorous evidence of supporting parents in
111 end-of-life decisions and care. As parental support is an important component of FCC,
112 the support of parents during EOLC has different perspectives and needs different
113 approaches. However, one cannot deliver poor EOLC while providing excellent FCC.

114 Both practices are interlinked. Therefore, our NICU is translating and implementing
115 FCC into EOLC practices.

116 In mainland China, parents are mostly the main decision-makers in withdrawing
117 life-sustaining treatments in infants and neonatologists often follow the wishes of the
118 parents. However, there is limited experience in supporting parents after the decision
119 is made to withdraw treatment. Therefore, the aim of this study was to develop a
120 family supportive EOLC intervention and to evaluate parent reported outcome
121 measures related to depression and satisfaction.

122 **MATERIALS AND METHODS**

123 This quasi-experimental study adopted a non-randomized controlled trial (non-RCT)
124 design because blinding was not possibly due to the nature and delivery of the
125 intervention. The study was registered in clinicaltrials.gov (approval number
126 NCT05270915). The study was conducted between 6th of May 2020 and 20th of
127 September 2021. The guideline ‘Evaluating complex interventions in end of life care:
128 the MORECare statement on good practice generated by a synthesis of transparent
129 expert consultations and systematic reviews’ was used to report this study (20).

130 **Setting**

131 The study setting was the tertiary NICU at the stand-alone Hunan Children’s Hospital
132 in Changsha, China. The 180-bed NICU department serves as a regional tertiary
133 center for all infants above 24 weeks gestational age requiring intensive care
134 treatment. Main causes of mortality in our NICU are congenital malformation,
135 preterm birth and septic shock. In 2020 and 2021, the annual NICU admission rate
136 was around 4000 infants. The annual mortality rate of the NICU in the past five years
137 was between 3-5%. Since the introduction of FCC in our NICU, parents are allowed
138 to visit the NICU in daytime (8.00-17.30hrs) and participate in basic care of their
139 infant and are supported by medical and nursing staff (17,20).

140 **Patient and Public Involvement and Engagement**

141 Before the study protocol was finalized, we organized a patient and public
142 involvement and engagement meeting with 15 parent couples with previous
143 experience in neonatology. The individual conversations with both mothers and
144 fathers of 15 infants were focused on the proposed study methods, intervention, and
145 outcome measures. Overall, most parents thought that their involvement in EOLC was
146 important to reduce depression during and after the death of their infant. Parents
147 indicated that they would value the support of NICU staff and would welcome a
148 separate room to stay with their baby in the final days of life. Most parents also
149 suggested having a psychologist in the NICU team and having their support at the
150 EOLC. In terms of follow-up, most parents indicated that they did not want a
151 long-term follow-up meeting or complete surveys one month after NICU discharge.
152 The suggestions of the parents were amended in the final study protocol.

153 **Study participants and recruitment**

154 Inclusion criteria were infants whose treatment was withdrawn at Corrected
155 Gestational Age (CGA) less than 28 days and their parents. The exclusion criteria
156 were infants with an expected time of death less than three hours after NICU
157 admission. Parents were excluded if they had mental illness or language issues that
158 might limit their integration and communication with the healthcare team.

159 After an end-of-life decision was made, a research nurse informed the parents about
160 the study. Participation was based on the parents' decision and after written consent.
161 The allocation of the infant and parents to the intervention or control group was
162 case-controlled based on the wishes of the parents. If parents wanted to stay in the
163 NICU with their infant during the EOLC pathway, parents were allocated to the
164 intervention group. If parents did not want to stay in the NICU during the EOLC
165 pathway, their infant would stay in our NICU and receive standard EOLC care.

166 **Standard care and Intervention**

167 The standard EOLC included the international guidance of palliative care and EOLC
168 in neonatology (21-23). In China, parents are often the decision-makers of their
169 infant's treatment and the NICU clinicians usually respect the parent's decision (24).
170 After parents have decided to withdraw treatment, standard EOLC is initiated and
171 includes monitoring of vital signs and withholding or withdrawing rescue procedures
172 such as intubation and intravenous infusion. Unnecessary lines are removed and pain
173 management is provided by analgesia. Comfort care is provided by nurses including
174 basic care such as skin care and oral care. After the infant died, the NICU physician
175 informs the parents by phone.

176 The intervention 'family supportive EOLC' was developed based on the
177 international guidelines of family-centered care (25) with additional aspects of care
178 and support. We designed a separated single-bedded EOLC room for the infant and
179 parents. Other family members, such as grandparents or siblings, were allowed to visit
180 the infant and parents. The design of the room included the option for parents to stay
181 comfortably on a sofa to relax and to play soothing music. Parents were encouraged to
182 stay as long as they want and participate in basic care including physical contact with
183 their infant. The nurses supported the parents in creating commemorative items such
184 as a 'Yuan man' box with photos, baby handprint cards, footprint cards, a lock of hair
185 and other precious memory items. A psychologist, in collaboration with our NICU,
186 and a neonatologist supported the parents by individual interviews on a daily basis to
187 listen to the concerns of parents and to provide emotional support. To ensure
188 consistency in delivering the intervention, the medical staff and psychologist were
189 trained in delivering the interviews and EOLC practices.

190 **Outcomes measures and data collection**

191 The primary outcomes were depression and satisfaction as reported by parents at one
192 week after infant's death. Because the Chinese version of the Edinburgh Postnatal
193 Depression Scale (EPDS) has not been validated among fathers, we decided to use the
194 Chinese version of the Hamilton Depression rating scale (HAMD) to evaluate
195 depression among fathers. The Chinese version of the EPDS was used to assess
196 depression among mothers (26-27). The HAMD includes 17 items with a 3 or 5-point
197 Likert answer option scale with a total score of 78 (28). The HAMD has been
198 translated and validated in Chinese. The internal consistency of the Chinese version
199 demonstrated a Cronbach's alpha of 0.646 (29). The EPDS is developed to measure
200 the depression of mothers after NICU (30). The scale includes 10 items with a 4-point
201 Likert answer option scale with a total score of 30. The EPDS has been translated and
202 validated in Chinese among mothers. The internal consistency of the Chinese version
203 has been adequate with a Cronbach's alpha of 0.76 (31).

204 Parent satisfaction was measured by the hospital standard parent satisfaction
205 survey completed by both parents. The parent satisfaction with care instrument was
206 our hospital standardized parents satisfaction with care questionnaire including 20
207 items using a 5-point Likert answer option scale with a total score of 100. It included
208 4 parts of medical treatment, medical staff's negotiation attitude, hospital settings and
209 social service. This scale is used among all parents in our hospital on a weekly basis
210 by an external company.

211 Basic parent and infant characteristics were collected from the medical charts.
212 Infants' characteristics included prenatal history, diagnoses, on-going therapy at time
213 of withdrawal of treatment. The parental characteristics included age, mode of
214 delivery, education and family income. The parental outcome measures, depression
215 and satisfaction, were collected one week after the death of the infants during a
216 face-to-face follow-up meeting in the hospital with the psychologist.

217 **Data analysis**

218 The statistical software package 'IBM Corp. Released 2013. IBM SPSS Statistics for
219 Windows, Version 22.0. Armonk, NY: IBM Corp' was used for the analysis. The
220 distribution of baseline characteristics for two groups are summarized using
221 descriptive statistical methods. Student t-test for continuous variables and the
222 Chi-square test for categorical variables were used to analyze the outcomes.

223 **Ethics**

224 Ethical approval was granted by the Ethics Committee of Hunan Children's Hospital
225 (HCHLL-2020-23). The study procedures adhered to the International Council for
226 Harmonization and Good Clinical Practice guidance (32) and the principles of the
227 Declaration of Helsinki (33). Parents were informed about the study objectives,
228 written informed consent was obtained, and parents were able to withdraw from
229 participation at any time.

230 **RESULT**

231 In total, 62 infants died in the NICU during the study period. Of these, 45 infants and
232 90 parents were screened and enrolled in the study (**Fig. 1**). The infants' average
233 gestational ages were smaller and birth weights were lower in the family supportive
234 EOLC group compared with the standard care group, but no significant differences
235 were observed (**Table 1**). The infants' gender did not significantly differ between both
236 groups (male: 12 vs 16, $p=0.783$). The most common causes of death were congenital
237 abnormalities in both group. The median age of death in the standard care group was
238 lower than in the family supportive EOLC group (**Table 1**). The main reasons of
239 treatment withdrawal were deficiency in family financial support (not able to pay the
240 additional hospital expenses), poor neurological prognosis and serious condition
241 (**Table 1**).

242 The characteristics of the 90 parents (45 mothers and 45 fathers) are presented in
243 **Table 2**. There were no differences in parent's age, way of delivery, and economic
244 status. Both the mothers and fathers in the family supportive EOLC groups had
245 significantly higher educational background compared to the parents in the standard
246 EOLC group (**Table 2**).

247 The outcomes of parental depression revealed differences in both mothers and
248 fathers between both groups (**Table 3**). The post-natal depression in mothers was
249 significant lower in the family supportive EOLC group compared to mothers in the
250 standard EOLC group (mean 6.90 vs 7.56; $p=0.017$). The depression among fathers in
251 the family supportive EOLC group were significantly lower compared to fathers in
252 the standard EOLC group (mean 20.7 vs 23.1; $p=0.001$). The outcomes of parent
253 satisfaction revealed differences in that parents in the family supportive EOLC group
254 showed higher satisfaction rates compare to the standard EOLC group (mean 88.9 vs
255 86.6; $p=0.001$).

256 **DISCUSSION**

257 To our knowledge, this is the first study to support parents during EOLC in mainland
258 China. The aim of our study was to test a family supportive EOLC intervention to
259 decrease depression among parents and increase parent satisfaction around the death
260 of their infant. The outcome of parent satisfaction with care can be considered an
261 important result. Although no standardized instruments are available to measure
262 satisfaction of EOLC, our hospital questionnaire was sensitive enough to demonstrate
263 differences of overall satisfaction scores between both groups of parents. Further
264 research is needed to develop robust instruments to measure the outcomes of EOLC
265 such as parent satisfaction.

266 The main cause of death among our included infants was congenital
267 malformations, which is consistent with other studies in China (34, 35). This is in
268 contrast with international studies reporting the main cause of death in neonatology is

269 related to premature birth and infection (36, 37). This difference might be due to the
270 location of our NICU situated in a stand-alone children's hospital. Infants born very
271 premature in other regions of our Hunan province might not have been transferred to
272 our center.

273 Parental presence during EOLC has been addressed as an important part in
274 neonatal care. The role of the NICU staff in EOLC is to support parents in their
275 mental health and well-being as well as empowering parents to take part in the care of
276 their infant during the last days of life (38). The international guideline of FCC in
277 neonatal, pediatric and adult intensive care suggests implementing strategies to
278 improve parental confidence and mental health during and after the NICU (39). In
279 China, the initial steps in implementing FCC in neonatology only started a few years
280 ago (16-18). However, there is limited evidence in FCC practices across the regions in
281 China (40, 41). Our study might contribute to identifying interventions that are
282 feasible and effective in Chinese NICUs who have started recently with FCC
283 practices.

284 Our study evaluate the family supportive EOLC intervention related to parent
285 depression. In our previous FCC intervention studies we were able to demonstrated
286 improvements in parental depression and anxiety (42, 43). Parents face psychological
287 distress in perinatal and neonatal death with an increased risk of post-traumatic stress
288 disorder, depression, and anxiety. Reports have identified the relationship between
289 perinatal death and the devastating impact on parents, including stress and mental
290 health issues lasting for at least six months after the death of their infant (44, 45).
291 During our parent consultation round to discuss our study protocol, parents indicated
292 that they did not want a six months follow-up survey. Therefore, we have no
293 follow-up data to inform any long-term support to parents in our community.

294 In our study, more parents opted for the standard EOLC. Perhaps this can be
295 described to a cultural issue that parents find it difficult in facing the end of life of
296 their infant. A review of Chinese hospice care identified that parents are afraid of
297 staying with their child and experienced more anxiety (46). The perspectives of
298 parents of EOLC in neonatology was explored in a qualitative study among 10 parents
299 (47). These parents indicated that it was extremely important to be able to stay in the
300 NICU regardless the diagnosis on their infant. This 'zero separation' has also be
301 addressed as an important issue during the recent two COVID-19 pandemic years (48,
302 49).

303 **Limitations**

304 A number of limitations of our study needs to be addressed. First, we used a non-RCT
305 design to provide parents the option to participate in the study. We provided parents
306 the option to choose in what study arm they wanted to participate based on the advice
307 of the parent consultation round before the start of the study. Secondly, the study
308 intervention was not blinded which can potentially influence the outcome measures.

309 The third limitation is that the study was performed at a single center with a small
310 sample size limiting the generalizability of the results for clinical practice. Forth, the
311 different instruments to measure depression among fathers and mothers limited the
312 comparison between the parent couples. Finally, our follow-up was 1 week after the
313 infants' death. Further research is needed to explore long-term impact on parents.

314 **Conclusion**

315 Neonatal death is still one of the major problems threatening the global health. Our
316 study indicated that providing a comfortable environment and supportive care to
317 parents during the final days of life of an infant decrease their depression and
318 increases parent satisfaction. The NICUs in mainland China and beyond might
319 consider to involve parents in EOLC by providing a single room, have a dedicated
320 psychologist available and provide supportive commemoration materials for parents
321 such as a 'yuan man' box.

322 **CONFLICT OF INTEREST**

323 The authors declare that the research was conducted in the absence of any commercial
324 or financial relationships that could be construed as a potential conflict of interest.

325 **AUTHORS' CONTRIBUTIONS**

326 Concept and design: Zhu Li-hui, Zhang Rong, Peng xiao-ming and Xiong yue-e, Jos
327 M. Latour. Data collection: Chen Mu-hua, Zhang Na, Tang qian, Chen ke-liang,
328 Zhang Rong. Statistical analysis: Tang qian, Zhang Na, Zhang Rong. Drafting of the
329 manuscript: Zhang Rong and Jos M Latour. Providing revisions of the manuscript for
330 important intellectual content: Zhu Li-hui, Peng xiao-ming and Xiong yue-e, Zhang
331 Na and Tang qian. All authors contributed to the article and approved the submitted
332 version.

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335 Hospital Research Foundation (number 202114) financially supported this work

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339 the study.

340 **DATA AVAILABILITY STATEMENT**

341 The raw data supporting the conclusions of this article will be made available by the
342 authors, without undue reservation.

343 **ETHICS STATEMENT**

344 Ethical approval of the study was granted by the Ethics Committee of Hunan
345 Children's Hospital (HCHLL-2020-23). The study procedures adhered to the
346 International Council for Harmonization and Good Clinical Practice guidance and the
347 principles of the Declaration of Helsinki. Parents were informed about the study
348 objectives, written informed consent was obtained, and parents were able to withdraw
349 from participation at any time.

350 **SUPPLEMENTARY MATERIAL**

351 Not applicable.

352 **Reference**

- 353 1. World Health Organization. World Health Statistics 2021. Monitoring health for the
354 SDGs.
355 <https://apps.who.int/iris/bitstream/handle/10665/342703/9789240027053-eng.pdf>
356 [accessed 2 January 2022].
- 357 2. National Health Commission of the People's Republic of China. China Health
358 Statistics Yearbook 2020 Beijing: Peking Union Medical College Press, 2021:215-218
- 359 3. World Health Organization. Palliative Care. Key Facts.
360 <https://www.who.int/news-room/fact-sheets/detail/palliative-care> [accessed 2 January
361 2022].
- 362 4. Worldwide Palliative Care Alliance and World Health Organization. Global atlas of
363 palliative care at the end of life. 2014. Connor SR, Bermedo MCS, (eds). London, UK.
364 https://www.who.int/nmh/Global_Atlas_of_Palliative_Care.pdf [accessed 2 January
365 2022].
- 366 5. Silverman WA. A hospice setting for humane neonatal death. *Pediatrics*.
367 1982;69(2):239.
- 368 6. Haug S, Dye A, Durrani S. End-of-Life Care for Neonates: Assessing and
369 Addressing Pain and Distressing Symptoms. *Front Pediatr*. 2020;24(8):574180.
370 <https://doi.org/10.3389/fped.2020.574180>
- 371 7. Mcdermott CL, Engelberg RA, Woo C. Novel data linkages to characterize
372 palliative and end-of-life care: challenges and considerations. *J Pain Symptom*
373 *Manage*. 2019;58(5):851-856. doi: 10.1016/j.jpainsymman.2019.07.017.
- 374 8. National Institute for Health and Care Excellent (NICE). End of life care for infants,
375 children and young people with life-limiting conditions: planning and management.
376 NICE guideline. 25 July 2019. www.nice.org.uk/guidance/ng61 [accessed 2 January
377 2022].
- 378 9. Dombrecht L, Beernaert K, Chambaere K, Cools F, Goossens L, Naulaers G, et al.
379 End-of-life decisions in neonates and infants : a population-level mortality
380 follow-back study. *Arch Dis Child Fetal Neonatal Ed*.
381 2021:fetalneonatal-2021-322108. doi: 10.1136/archdischild-2021-322108. Online
382 ahead of print.
- 383 10. Veldhuijzen ZS, Ferretti E, MacLean G, Daboval T, Lauzon L, Reuvers E, et
384 al. Medications to manage infant pain, distress and end-of-life symptoms in the
385 immediate postpartum period. *Expert Opin Pharmacother*. 2022;23(1):43-48. doi:
386 10.1080/14656566.2021.1965574.

- 387 11. Allen JD, Shukla R, Baker R, Slaven JE, Moody K. Improving Neonatal Intensive
388 Care Unit Providers' Perceptions of Palliative Care through a Weekly Case-Based
389 Discussion. *Palliat Med Rep*. 2021;2(1):93-100. doi: 10.1089/pmr.2020.0121
- 390 12. Chen X, Li H, Song J, Sun P, Lin B, Zhao J, et al. The Resuscitation of Apparently
391 Stillborn Neonates: A Peek Into the Practice in China. *Front Pediatr*. 2020;2(8):231.
392 <https://doi.org/10.3389/fped.2020.00231>
- 393 13. Kim S, Savage TA, Hershberger PE, Kavanaugh K. End-of-Life Care in Neonatal
394 Intensive Care Units from an Asian Perspective: An Integrative Review of the
395 Research Literature. *J Palliat Med*. 2019;22(7):848-857.
396 <https://doi.org/10.1089/jpm.2018.0304>
- 397 14. Chen CH, Huang LC, Liu HL, Lee HY, Wu SY, Chang YC, et al. To explore the
398 neonatal nurses' beliefs and attitudes towards caring for dying neonates in Taiwan.
399 *Matern Child Health J*. 2013;17(10):1793-801. doi: 10.1007/s10995-012-1199-0.
- 400 15. Huang LC, Chen CH, Liu HL, Lee HY, Peng NH, Wang TM et al. The attitudes of
401 neonatal professionals towards end-of-life decision-making for dying infants in
402 Taiwan. *J Med Ethics*, 2013;39(6):382-6.
403 <https://doi.org/10.1136/medethics-2011-100428>
- 404 16. Zhang R, Huang RW, Gao XR, Peng XM Peng, Zhu LH, Rangasamy R, Latour
405 JM. Involvement of Parents in the Care of Preterm Infants: A Pilot Study Evaluating a
406 Family-Centered Care Intervention in a Chinese Neonatal ICU. *Pediatr Crit Care
407 Med*. 2018;19(8):741-747. doi: 10.1097/PCC.0000000000001586.
- 408 17. Lv B, Gao XR, Sun J, Li TT, Liu ZY, Zhu LH, Latour JM. Family-Centered Care
409 Improves Clinical Outcomes of Very-Low-Birth-Weight Infants: A
410 Quasi-Experimental Study. *Front Pediatr*. 2019;12(7):138.
411 <https://doi.org/10.3389/fped.2019.00138>
- 412 18. He SW, Xiong YE, Zhu LH, Lv B, Gao XR, Latour JM. Impact of family
413 integrated care on infants' clinical outcomes in two children's hospitals in China: a
414 pre-post intervention study. *Ital J Pediatr*. 2018;44(1):65.
415 <https://doi.org/10.1186/s13052-018-0506-9>
- 416 19. Ding X, Zhu L, Zhang R, Wang L, Wang TT, Latour JM. Effects of family-centred
417 care interventions on preterm infants and parents in neonatal intensive care units: A
418 systematic review and meta-analysis of randomised controlled trials. *Aust Crit Care*.
419 2019;32(1):63-75. doi: 10.1016/j.aucc.2018.10.007.
- 420 20. Higginson IJ, Evans CJ, Grande G, Preston N, Morgan M, MORECare.
421 Evaluating complex interventions in end of life care: the MORECare statement on
422 good practice generated by a synthesis of transparent expert consultations and
423 systematic reviews. *BMC Med*. 2013;24(11):111. doi: 10.1186/1741-7015-11-111.

- 424 21. Mancini A, Uthaya S, Beardsley C, Wood D, Modi N. Practical Guidance for the
425 Management of Palliative Care on Neonatal Units, 1st edn. London: Chelsea and
426 Westminster Hospital NHS Foundation Trust, 2014. Available from:
427 <https://www.chelwest.nhs.uk/services/childrens-services/neonatal-services/links/Practical-guidance-for-the-management-of-palliative-care-on-neonatal-units-Feb-2014.pdf>
428 [accessed 2 January 2022].
429
- 430 22. Cole A, Craig F, Daly C, English S, George S, Gill B, et al. Palliative Care
431 (Supportive and End of Life Care): A Framework for Clinical Practice in Perinatal
432 Medicine. London: British Association of Perinatal Medicine, 2010. Available from:
433 https://hubble-live-assets.s3.amazonaws.com/bapm/file_asset/file/72/Palliative_care_final_version_Aug10.pdf [accessed 26 January 2022].
434
- 435 23. Palliative Care Australia. Standards for Providing Quality Palliative Care for All
436 Australians. Deakin West: Palliative Care Australia, 2005. Available from:
437 <https://palliativecare.org.au/wp-content/uploads/2015/07/Standards-for-providing-quality-palliative-care-for-all-Australians.pdf> [accessed 26 January 2022]
438
439
- 440 24. Li SP, Chen PY. The strategy of treatment abandonment in NICU. *Medicine*
441 *Philosophy*. 2007;6(28):66-67.
- 442 25. Davidson JE, Aslakson RA, Long AC, Kathleen AP, Erin KK, Joanna H, et al.
443 Guidelines for Family-Centered Care in the Neonatal, Pediatric, and Adult ICU. *Crit*
444 *Care Med*. 2017;45(1):103-128. doi: 10.1097/CCM.0000000000002169.
- 445 26. Maurer DM, Raymond TJ, Davis BN. Depression: Screening and Diagnosis. *Am*
446 *Fam Physician*. 2018; 98(8):508-515.
- 447 27. Ijaz S, Davies P, Williams CJ, Kessler D, Lewis G, Wiles N. Psychological
448 therapies for treatment-resistant depression in adults. *Cochrane Database Syst Rev*.
449 2018;5(5):CD010558. doi: 10.1002/14651858.CD010558.pub2.
- 450 28. Nixon N, Guo B, Garland A, Kaylor-Hughes C, Nixon E, Morriss R. The bi-factor
451 structure of the 17-item Hamilton Depression Rating Scale in persistent major
452 depression; dimensional measurement of outcome. *PLoS One*. 2020;15(10):e0241370.
453 doi: 10.1371/journal.pone.0241370.
- 454 29. Li WB, Xu MZ, Gao YL. The validity and reliability of the Hamilton Depression
455 Rating Scale. *Chin J Nerv Ment Dis*. 2006;2(32):118-120.
- 456 30. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development
457 of the 10-item Edinburgh postnatal depression scale. *Br J Psychiatry*.
458 1987;150(6):782–786. doi: 10.1192/bjp.150.6.782.

- 459 31. Guo XJ, Wang YQ, Chen J. Study on the efficacy of the Edinburgh postnatal
460 depression scale in puerperas in Chengdu. *Chin J Pract Nurs*. 2009;1(25):4-6. doi:
461 10.3760/cma.j.issn.1672-7088.2009.01.002.
- 462 32. Good Clinical Practice Network. ICH harmonised guideline integrated addendum
463 to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) ICH Consensus
464 Guideline. Retrieved from: <https://ichgcp.net/> [accessed 19 December 2021]
- 465 33. World Medical Association. Declaration of Helsinki-Ethical Principles for Medical
466 Research Involving Human Subjects. (2018) Retrieved from:
467 [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-
468 -medical-research-involving-human-subjects/](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) [accessed 19 December 2021]
- 469 34. Dong HF, Li WL, Xu FL, Li DL, Li L, Wang XC, et al. Investigation of in-patient
470 neonatal death at 18 hospitals in Henan Province. *Chin J Perinat Med*.
471 2019;6(22):412-419. doi: 10.3760/cma.j.issn.1007-9408.2019.06.008
- 472 35. Xu FD, Kong XY, Feng ZC. Mortality rate and cause of death in hospitalized
473 neonates: an analysis of 480 cases. *Chin J Contemp Pediatr*. 2017;2(19):152-158. doi:
474 10.7499/j.issn.1008-8830.2017.02.005.
- 475 36. Veloso FCS, Kassar LML, Oliveira MJC, Lima THB, Bueno NB, Gurgel RQ, et al.
476 Analysis of neonatal mortality risk factors in Brazil: a systematic review and
477 meta-analysis of observational studies. *J Pediatr (Rio J)*. 2019;95(5):519-530. doi:
478 10.1016/j.jpmed.2018.12.014.
- 479 37. Lona Reyes JC, Pérez Ramírez RO, Llamas Ramos L, Gómez Ruiz LM, Benítez
480 Vázquez EA, Rodríguez Patino V. Neonatal mortality and associated factors in
481 newborn infants admitted to a Neonatal Care Unit. *Arch Argent Pediatr*.
482 2018;116(1):42-48. doi: 10.5546/aap.2018.eng.42.
- 483 38. Krishelle LA, Nancy KE. Primary palliative care in neonatal intensive care. *Semin*
484 *Perinatol*. 2017;41(2):133-139. doi: 10.1053/j.semperi.2016.11.005.
- 485 39. McGrath JM, Wool C, Black BP, Leuthner SR, Jones EL, Muñoz-Blanco S, et al.
486 Chapter 15. Attending to pain and suffering in palliative care. In: Limbo R, Wool C,
487 Carter B, editors. *Handbook of Perinatal and Neonatal Palliative Care*, 1st Ed. New
488 York, NY: Springer Publishing Company. (2020) 234–253.
- 489 40. Yi YZ, Su T, Jia YZ, Xue Y, Chen YZ, Zhang QS, et al. Family-centered care
490 management strategies for term and near-term neonates with brief hospitalization in a
491 level III NICU in Shenzhen, China during the time of COVID-19 pandemic. *J Matern*
492 *Fetal Neonatal Med*. 2021;22:1-4. doi: 10.1080/14767058.2021.1902499.

- 493 41. Li XY, Lee S, Yu HF, Ye XY, Warre R, Liu XH, et al. Breaking down barriers:
494 enabling care-by-parent in neonatal intensive care units in China. *World J Pediatr.*
495 2017;13(2):144-151. doi: 10.1007/s12519-016-0072-4.
- 496 42. Baughcum AE, Fortney CA, Winning AM, Dunnells ZDO, Humphrey LM,
497 Gerhardt CA. Healthcare Satisfaction and Unmet Needs Among Bereaved Parents in
498 the NICU. *Adv Neonatal Care.* 2020;20(2):118-126.
499 doi:10.1097/ANC.0000000000000677.
- 500 43. Lacasse JR, Cacciatore J. Prescribing of psychiatric medication to bereaved
501 parents following perinatal/neonatal death: an observational study. *Death Stud.*
502 2014;38(6-10):589-96. doi:10.1080/07481187.2013.820229.
- 503 44. Youngblut JM, Brooten D. Comparison of mothers and grandmothers physical
504 and mental health and functioning within 6 months after child NICU/PICU death.
505 *Ital J Pediatr.* 2018;44(1):89. <http://doi:10.1186/s13052-018-0531-8>
- 506 45. Baransel ES, Uçar T. Posttraumatic stress and affecting factors in couples after
507 perinatal loss: A Turkish sample. *Perspect Psychiatr Care.* 2020;56(1):112-120. doi:
508 10.1111/ppc.12390
- 509 46. Huang J, Song ZZ. The current situation and progress of hospice care in China. *J*
510 *Mod Med Health.* 2020;2(36):214-216. doi: 10.3969/j.issn.1009-5519.2020.02.016.
- 511 47. Currie ER, Christian BJ, Hinds PS, Perna SJ, Robinson C, Day S, et al. Parent
512 Perspectives of Neonatal Intensive Care at the End-of-Life. *J Pediatr Nurs.*
513 2016;31(5):478-89. doi: 10.1016/j.pedn.2016.03.023.
- 514 48. Ryan L, Plötz FB, van den Hoogen A, Latour JM, Degtyareva M, Keuning M, et
515 al. Neonates and COVID-19: state of the art : Neonatal Sepsis series. *Pediatr Res.*
516 2022;91(2):432-439. doi: 10.1038/s41390-021-01875-y.
- 517 49. Kostenzer J, Zimmermann LJI, Mader S; EFCNI COVID-19 Zero Separation
518 Collaborative Group. Zero separation: infant and family-centred developmental care
519 in times of COVID-19. *Lancet Child Adolesc Health.* 2022;6(1):7-8. doi:
520 10.1016/S2352-4642(21)00340-0.

521

522 **Table 1.** Infants' characteristics

523

| Infants | Family supportive EOLC (n=20) | Standard EOLC (n=25) | P value |
|------------------------------------------------------------|------------------------------------------|---------------------------------|----------------|
| Gender, male; n (%) | 12 (60) | 16 (64) | 0.783 |
| Gestational age in weeks; mean (SD) | 31.45 (5.18) | 33.8 (5.56) | 0.234 |
| Birth weight in grams; mean (SD) | 1677 (974.2) | 2179 (1060.3) | 0.302 |
| Length of stay in days; mean (SD) | 16.7 (27.5) | 16.7 (28.0) | 0.828 |
| Age at death in days; mean (SD) | 30.8 (37.2) | 23.9 (32.6) | 0.710 |
| Days from withdraw decision to death in days; mean (SD) | 0.4 (0.68) | 0.36 (1.25) | 0.540 |
| Location of infant's birth; n (%) | | | |
| City | 8 (40) | 6 (24) | 0.463 |
| Town | 4 (20) | 3 (12) | |
| Village | 8 (40) | 16 (64) | |
| Major cause of death; n (%) | | | |
| Respiratory failure | (10) | 1 (4) | 0.913 |
| Congenital abnormalities | 9 (45) | 11 (44) | |
| Hypoxic-ischaemic encephalopathy | 2 (10) | 2 (8) | |
| Necrotising enterocolitis | 2 (10) | (8) | |
| Prematurity | 2 (10) | 1 (4) | |
| Septic shock | 1 (5) | 3 (12) | |
| Hematology disease | 1 (5) | 2 (8) | |
| MODS | 1 (5) | 3 (12) | |
| Reason to withdraw decision; n (%) | | | |
| Economic level | 3 (15) | 4 (16) | 0.405 |
| Poor prognosis | 6 (30) | 12 (48) | |
| Infants' critical ill condition | 11 (55) | 9 (36) | |

524 EOLC=End of life care; MODS=multiply organ dysfunction syndrome; SD=Standard
525 Deviation.

526 **Table 2.** Parents' characteristics

527

| Parents | Family supportive EOLC (n=20) | Standard EOLC (n=25) | P value |
|----------------------------------|----------------------------------------------|-------------------------------------|----------------|
| Mothers' age; mean (SD) | 31.6 (5.41) | 29.8 (5.29) | 0.785 |
| Delivery, vaginal; n (%) | 11 (55) | 12 (48) | 0.641 |
| Mother's education degree; n (%) | | | |
| Above university level | 14 ^a (70) | 8 ^b (32) | |
| High school level | 2 ^a (10) | 10 ^b (40) | 0.026* |
| Primary school level | 4 ^a (20) | 7 ^a (28) | |
| Father's age; mean (SD) | 34.5 (7.47) | 31.6 (5.54) | 0.818 |
| Father's education degree; n (%) | | | |
| Above university level | 13 ^a (65) | 6 ^b (24) | |
| High school level | 3 ^a (15) | 10 ^a (40) | 0.020* |
| Primary school level | 4 ^a (20) | 9 ^a (36) | |
| Family income level; n (%) | | | |
| <3000(¥) | 6 (30) | 4 (16) | |
| 3000-6000(¥) | 9 (45) | 11 (44) | 0.471 |
| >6000(¥) | 5 (25) | 10 (40) | |

528 ^{a,b}; the labels are automatically generated by the Bonferroni correction method when
529 comparing the two groups. When the same letter (^a) is included in the same group, the
530 difference between the two groups is not statistically significant. When ^a and ^b are included in
531 the same group, the difference between the two groups is statistically significant.*; represents
532 chi-square test.

533 ¥=RMB per month; EOLC=End of life care; SD=Standard Deviation.

534| **Table 3.** Parental depression (mothers and fathers) one week after infant's death (n=45)
 535|

| Group | Cases (n) | EPDS (mothers) | HAMD (fathers) | Satisfaction |
|--------------------------------------|----------------------|---------------------------|---------------------------|---------------------|
| Family supportive EOLC (mean and SD) | 20 | 6.90 ±0.91 | 20.7 ±2.05 | 88.9 ±1.98 |
| Standard EOLC (mean and SD) | 25 | 7.56 ±0.87 | 23.1 ±2.28 | 86.6 ±2.04 |
| t | | 2.476 | 3.696 | -3.659 |
| P value | | 0.017 | <0.001 | <0.001 |

536 EOLC=End of life care; EPDS=Edinburgh Postnatal Depression Scale; HAMD=Hamilton
 537 Depression rating scale; SD=Standard Deviation.
 538538

Figure 1. Study Flow Chart

539

