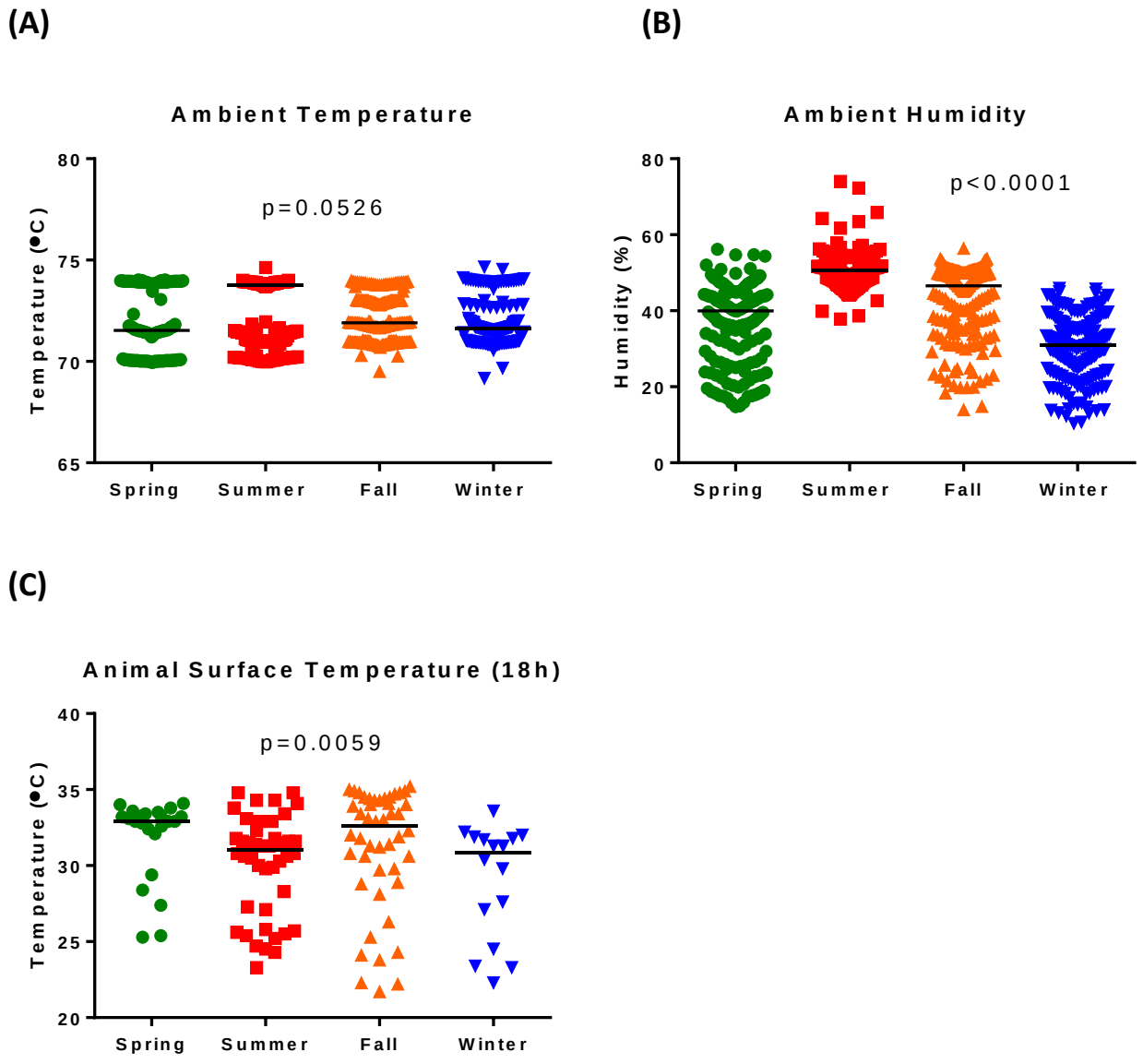

Supplemental Figure 1 Graph shows values and median for (A) ambient temperature and (B) ambient humidity in the animal housing room, and (C) animal surface temperatures at 18h post-CLP.

Supplemental Table 1 Summary of the prior literature on gender-effects in clinical sepsis

	reference	Findings
1	Schroder, J. et al. Gender differences in human sepsis. Arch. Surg. 133, 1200-1205 (1998).	Reported improved survival and increased levels of anti-inflammatory mediators in female vs. male patients with sepsis.
2	Eachempati, S.R. et al. Gender-based differences in outcome in patients with sepsis. Arch. Surg. 134, 1342-1347 (1999).	Reported improved survival in male vs. female patients with surgical sepsis.
3	Adrie, C., et al. Influence of gender on the outcome of severe sepsis: a reappraisal. Chest 132, 1786-1793 (2007).	Reported improved survival in female vs. male patients with sepsis.
4	Pietropaoli, A.P. et al. Gender differences in mortality in patients with severe sepsis or septic shock. Gend. Med. 7, 422-437 (2010).	Reported increased in-hospital mortality in female vs. male patients with sepsis.
5	Nachtigall, I., et al. Gender-related outcome difference is related to course of sepsis on mixed ICUs: a prospective, observational clinical study. Crit. Care 15, R151 (2011).	Reported similar sepsis survival between the genders.
6	Madsen, T.E., et al. The DISPARITY Study: do gender differences exist in Surviving Sepsis Campaign resuscitation bundle completion, completion of individual bundle elements, or sepsis mortality? J. Crit. Care 29, 473.e477-411 (2014).	Reported similar in-hospital sepsis mortality between the genders.
7	Nasir, N., et al. Mortality in Sepsis and its relationship with Gender. Pak J. Med. Sci. 31, 1201-1206 (2015).	Reported improved sepsis survival and lower IL-6 levels in female vs. male patients with sepsis.
8	van Vught, L.A., et al. Association of Gender With Outcome and Host Response in Critically Ill Sepsis Patients. Crit. Care Med. 45, 1854-1862 (2017).	Reported similar sepsis survival between the genders.
9	Al Abbasi, B., et al. Implementation of the Surviving Sepsis Campaign in Patients With Heart Failure: Gender-Specific Outcomes. Cureus 12, e9140 (2020).	Reported similar sepsis survival between the genders.
10	Cerceo, E. et al. Association of gender, age, and race on renal outcomes and mortality in patients with severe sepsis and septic shock. J. Crit. Care 61, 52-56 (2021).	Reported improved survival and better renal outcomes in female vs male patients.

Supplemental Table 2 Summary of the prior literature on sex-effects in animal models of sepsis

	reference	Findings
1	Zellweger, R. et al. Females in proestrus state maintain splenic immune functions and tolerate sepsis better than males. Crit. Care Med. 25, 106-110 (1997).	Reported that proestrus female mice had improved sepsis survival in comparison to males.
2	Diodato, M.D. et al.. Gender differences in the inflammatory response and survival following haemorrhage and subsequent sepsis. Cytokine 14, 162-169 (2001).	Reported that female mice have improved sepsis survival in comparison to males, following a 2-hit model (hemorrhage and sepsis).
3	Knöferl, M.W. et al. Female sex hormones regulate macrophage function after trauma-hemorrhage and prevent increased death rate from subsequent sepsis. Ann. Surg. 235, 105-112 (2002).	Reported that proestrus female mice have improved sepsis survival in comparison to males, dependent on sex hormones (intact ovaries).
4	Hildebrand, F. et al. The importance of systemic cytokines in the pathogenesis of polymicrobial sepsis and dehydroepiandrosterone treatment in a rodent model. Shock 20, 338-346 (2003).	Reported that dehydroepiandrosterone (sex hormone precursor) reduced sepsis mortality in mice.
5	Dienstknecht, T. et al. Sex steroid-mediated regulation of macrophage/monocyte function in a two-hit model of trauma-hemorrhage and sepsis. Cytokine 25, 110-118 (2004).	Reported that 17beta-estradiol (female sex hormone) prevented immune dysfunction in castrated male mice subject to a 2-hit model (hemorrhage and sepsis).
6	Erikoğlu, M. et al. Effects of gender on the severity of sepsis. Surg. Today 35, 467-472 (2005).	Reported that female rats subject to sepsis exhibited less liver and lung damage in comparison to males.
7	Cotroneo, T.M., et al. Effects of buprenorphine on a cecal ligation and puncture model in C57BL/6 mice. J. Am. Assoc. Lab Anim. Sci. 51, 357-365 (2012).	Reported that buprenorphine reduced survival in male, but not female mice with sepsis.
8	Wehrenpfennig, P. et al. Mouse model of posttraumatic abdominal sepsis: survival advantage of females over males does not depend on the cecum size. Eur. Surg. Res. 52, 83-89 (2014).	Reported that female mice have improved sepsis survival in comparison to males, independent of cecum size.
9	Chen, J. et al. Gender dimorphism of the cardiac dysfunction in murine sepsis: signalling mechanisms and age-dependency. PLoS One 9, e100631 (2014).	Reported gender dimorphisms in sepsis-induced cardiac dysfunction.
10	Barter, J. et al. Age and Sex Influence the Hippocampal Response and Recovery Following Sepsis. Mol. Neurobiol. 56, 8557-8572 (2019).	Reported reduced cytokine production in male vs. female septic mice, and a prolonged hippocampal response in older male mice.
11	Luptak, I. et al. Myocardial Redox Hormesis Protects the Heart of Female Mice in Sepsis. Shock 52, 52-60 (2019).	Reported gender dimorphisms in sepsis-induced cardiac dysfunction, with protection in females.
12	Drechsler, S. et al. Relationship between age/gender-induced survival changes and the magnitude of inflammatory activation and organ dysfunction in post-traumatic sepsis. PLoS One 7, e51457 (2012).	Reported that female mice have improved sepsis survival in comparison to males, among young, middle aged and mature mice.
13	Efron, P.A. et al. Sex differences associate with late microbiome alterations after murine surgical sepsis. J. Trauma Acute care Surg. (2022).	Reported gender dimorphisms in sepsis-induced alterations of the microbiome in mice.
14	MacMillan-Crow, L.A. & Mayeux, P.R. Female mice exhibit less renal mitochondrial injury but greater mortality using a comorbid model of experimental sepsis. Internal medicine review (Washington, D.C. : Online) 4(2018).	Reported reduced survival, but attenuated mitochondrial injury in female vs. male septic mice.

Supplemental Table 3: Summary of the prior literature on the effects of advanced age on sepsis.

CLINICAL STUDIES		
1	Tran, D.D. et al. Age, chronic disease, sepsis, organ system failure, and mortality in a medical intensive care unit. Crit. Care Med. 18, 474-479 (1990).	Reported increased mortality in older patients with sepsis.
2	Martin, G.S. et al. The effect of age on the development and outcome of adult sepsis. Crit. Care Med. 34, 15-21 (2006).	Reported increased mortality in older patients with sepsis.
3	Yang, Y. et al. The effect of comorbidity and age on hospital mortality and length of stay in patients with sepsis. J. Crit. Care 25, 398-405 (2010).	Reported increased mortality in older patients with sepsis.
4	Rowe, T. et al. Outcomes of Older Adults With Sepsis at Admission to an Intensive Care Unit. Open Forum Infect. Dis. 3, ofw010 (2016).	Reported increased mortality in older patients with sepsis.
5	Brakenridge, S.C. et al. The impact of age on the innate immune response and outcomes after severe sepsis/septic shock in trauma and surgical intensive care unit patients. J. Trauma Acute care Surg. 85, 247-255 (2018).	Reported increased mortality in older patients with sepsis, associated with an immunophenotype of persistent immunosuppression and catabolism.
6	Kotfis, K. et al. A worldwide perspective of sepsis epidemiology and survival according to age: Observational data from the ICON audit. J. Crit. Care 51, 122-132 (2019).	Reported increased mortality in older patients with sepsis.
7	Wardi, G. et al. Age-related incidence and outcomes of sepsis in California, 2008-2015. J. Crit. Care 62, 212-217 (2021).	Reported increased mortality in older patients with sepsis.
ANIMAL STUDIES		
8	Turnbull, I.R. et al. Effects of age on mortality and antibiotic efficacy in cecal ligation and puncture. Shock 19, 310-313 (2003).	Reported increased mortality in aged vs young mice, associated with altered local inflammation.
9	Drechsler, S. et al. Relationship between age/gender-induced survival changes and the magnitude of inflammatory activation and organ dysfunction in post-traumatic sepsis. PLoS One 7, e51457 (2012).	Reported increased mortality in aged vs. young mice.
10	Nacionales, D.C. et al. Aged mice are unable to mount an effective myeloid response to sepsis. J. Immunol. 192, 612-622 (2014).	Reported that aged mice had increased sepsis mortality vs. young mice, associated with an altered innate immune response.
11	Gentile, L.F. et al. Protective immunity and defects in the neonatal and elderly immune response to sepsis. J. Immunol. 192, 3156-3165 (2014).	Reported increased mortality in aged vs. young mice.
12	Coletta, C. et al. Endothelial dysfunction is a potential contributor to multiple organ failure and mortality in aged mice subjected to septic shock: preclinical studies in a murine model of cecal ligation and puncture. Crit. Care 18, 511 (2014).	Reported that aged mice showed exacerbated endothelial dysfunction and increased sepsis mortality rates.
13	Starr, M.E. et al. Increased coagulation and suppressed generation of activated protein C in aged mice during intra-abdominal sepsis. Am. J. Physiol. Heart Circ. Physiol. 308, H83-91 (2015).	Reported that aged mice had increased sepsis mortality vs. young mice, associated with Increased coagulation and suppressed generation of activated protein C.
14	Cyr, A. et al. Circulating Metabolomic Analysis following Cecal Ligation and Puncture in Young and Aged Mice Reveals Age-Associated Temporal Shifts in Nicotinamide and Histidine/Histamine Metabolic Pathways. Oxid. Med. Cell. Longev. 2021, 5534241 (2021).	Reported that aged mice had increased sepsis mortality vs. young mice, associated with an altered metabolomics response.