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Admission interleukin-6 and carbapenemase carriage independently predict 30-day mortality in female Fournier's gangrene: a multicenter cohort

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ABSTRACT

Background: Female Fournier's gangrene (FG) is an underrecognized obstetric and gynecologic infectious emergency that frequently arises from vulvar, Bartholin gland, and episiotomy-related sources and carries high mortality. Rising multidrug resistance threatens standard empirical antibiotic regimens, yet female-specific data integrating inflammatory biomarkers with the genomic resistome are scarce.
Objective: To identify independent predictors of 30-day mortality and characterize the genomic resistome in women with FG to inform targeted broad-spectrum therapy.
Methods: In this multicenter retrospective cohort at two tertiary referral hospitals in Palembang, Indonesia (January 2020–December 2025), 42 women with surgically confirmed FG were studied. Admission interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), procalcitonin (PCT), and C-reactive protein (CRP) were measured; deep-tissue isolates underwent culture, broth-microdilution MIC testing, and multiplex PCR/next-generation sequencing for resistance genes. Multivariable logistic regression, ROC analysis, and Kaplan-Meier/Cox modeling were performed.
Results: Thirty-day mortality was 26.2% (95% CI 15.3–41.1), and infections were polymicrobial in 85.7%. Non-survivors had markedly higher admission IL-6 (485.2 vs 142.5 pg/mL; p<0.001; Cohen's d=2.58) and PCT (18.6 vs 4.2 ng/mL; p<0.001). IL-6 predicted mortality with an AUC of 0.93 (95% CI 0.83–0.99), outperforming LRINEC (AUC 0.69). Independent predictors were carbapenemase-producing isolates (adjusted OR 4.15, 95% CI 1.85–9.20; p=0.001) and admission IL-6 ≥300 pg/mL (adjusted OR 3.80, 95% CI 1.62–8.85; p=0.002). Resistome-concordant empirical therapy was associated with lower mortality (modeled NNT 3).
Conclusion: Admission IL-6 and carbapenemase carriage independently predicted 30-day mortality in this female FG cohort. Rapid biomarker and resistome screening may support risk stratification and empirical coverage in high-resistance tertiary settings, but prospective external validation is required before practice adoption.

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1. Introduction

Fournier's gangrene (FG) is a fulminant, rapidly progressive necrotizing fasciitis of the perineal, genital, and perianal region that remains a surgical and infectious emergency with contemporary mortality of approximately 20–30% despite modern critical care.[1-3] Mortality escalates sharply with advancing age, diabetes mellitus, septic shock, and delayed source control.[4-5] Although FG has traditionally been regarded as male-predominant, female FG is increasingly recognized and is associated with disproportionately high mortality, in part because deep pelvic and vulvoperineal anatomy produces atypical, often subtle early presentations that delay diagnosis and definitive debridement.[6] In lower-middle-income Asian settings, including Indonesia, this burden is amplified by a high prevalence of diabetes and frequently constrained access to early surgical and microbiological services.[7-8]

The pathophysiology of FG centers on synergistic polymicrobial invasion of fascial planes, in which aerobic and anaerobic organisms act together to produce obliterative endarteritis, microthrombosis, tissue hypoxia, and rapid liquefactive necrosis.[6,9] This microbial assault provokes a dysregulated innate immune response in which pathogen-associated molecular patterns stimulate macrophage release of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which in turn drive hepatic synthesis of C-reactive protein (CRP) and procalcitonin (PCT).[10-11] The magnitude of this early cytokine surge mirrors the extent of tissue destruction and the likelihood of progression to septic shock and multi-organ dysfunction, making admission biomarkers attractive candidates for objective risk stratification.[10,12]

For obstetrics and gynecology, the distinctive feature of female FG is its origin: a substantial proportion of cases arise from genital and obstetric sources, including Bartholin gland abscess, vulvar and perianal sepsis, and episiotomy or perineal-tear tract infection.[6] This establishes FG as a genuine, if under-appreciated, obstetric and gynecologic infectious morbidity rather than a purely urological or general-surgical entity. Despite this, female-specific evidence linking the clinical source profile to microbiological and molecular outcomes is sparse, and most prognostic data are extrapolated from predominantly male cohorts.[6,13]

Clinically, female FG seldom presents as overt necrotizing fasciitis; it more often masquerades as a simple Bartholin abscess, a slow-to-heal episiotomy or perineal-tear wound, postpartum perineal sepsis, or a vulvar cellulitis unresponsive to oral antibiotics, so the diagnosis is frequently entertained only once systemic toxicity supervenes.[6] The bedside red flags that should prompt urgent surgical exploration are pain disproportionate to visible findings, rapid centrifugal spread, dusky discoloration or bullae, crepitus, and early systemic toxicity out of keeping with local signs. Because the interval from presentation to definitive debridement is among the most modifiable determinants of survival,[14] an objective admission-available signal of high risk has direct and time-sensitive therapeutic value.

Early recognition is the single most important determinant of

survival, yet the clinical signs of necrotizing infection are frequently deceptive in women with deep vulvoperineal involvement.[6] The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was devised to flag necrotizing infection from routine laboratory variables, but prospective validation demonstrates only moderate, setting-dependent sensitivity and specificity, limiting its value as a standalone prognostic instrument.[15-16] These limitations have prompted interest in quantitative inflammatory biomarkers such as IL-6, PCT, TNF-α, and CRP as objective adjuncts available at admission.[11-12] In parallel, culture-independent molecular platforms, including multiplex polymerase chain reaction (PCR) and targeted next-generation sequencing (NGS), now enable rapid pathogen identification and resistance-gene (resistome) detection, shortening the interval to organism-directed therapy.[17-18]

The therapeutic landscape is being reshaped by antimicrobial resistance. Source control through aggressive, repeated surgical debridement together with prompt empirical broad-spectrum antibiotics remains the management cornerstone.[14] However, the global expansion of extended-spectrum beta-lactamase (ESBL)- and carbapenemase-producing Enterobacterales, which is particularly pronounced in Indonesian and Asia-Pacific tertiary units, increasingly renders standard empirical regimens such as a third-generation cephalosporin plus metronidazole inadequate.[19-21] Contemporary practice therefore favors a transition from empirical to resistance-mechanism-directed therapy, a strategy that depends critically on rapid resistome characterization and on local epidemiological data that are currently lacking for Indonesian obstetric and gynecologic practice.[17-18]

Against this background, we conducted a multicenter cohort study of women with FG at two tertiary referral hospitals in Palembang, Indonesia. We aimed to (i) characterize the admission inflammatory biomolecular profile and its association with 30-day mortality, (ii) map the genomic resistome of deep-tissue isolates, and (iii) identify independent predictors of mortality to inform a shift from empirical toward targeted, resistome-guided broad-spectrum antibiotic stewardship. We hypothesized that admission IL-6 and carbapenemase carriage would independently predict 30-day mortality and would outperform the LRINEC score for risk stratification.

2. Methods

Study design and setting. This was a multicenter retrospective observational cohort study conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. Patients were managed at two tertiary referral hospitals in Palembang, Indonesia, over a six-year period from January 2020 to December 2025. Both institutions are high-volume centers receiving complex obstetric, gynecologic, and surgical referrals; institutional identifiers are withheld to preserve confidentiality.

Case finding and patient flow. Cases were identified by cross-referencing operating-room logs, microbiology records, and discharge diagnostic codes for necrotizing soft-tissue infection across both centers for the full study period. Of the women screened, those without surgically confirmed vulvoperineal FG, with extra-pelvic disease, or with incomplete microbiological or biomolecular records were excluded, leaving 42 for analysis. Included and excluded patients did not differ materially in age or diabetes prevalence. Between-center counts were compared to assess heterogeneity; case mix and crude mortality were similar across the two hospitals.

Participants. Consecutive adult women (aged ≥18 years) with a clinical and intraoperative diagnosis of FG of the vulvar, perineal, or perianal region and available deep-tissue cultures from the initial debridement were eligible. The primary outcome was all-cause 30-day mortality; secondary outcomes were the inflammatory biomarker profile, the genomic resistome, and the number of serial debridements.

Sample size and power. The available six-year census yielded 42 eligible women. For the primary comparison of admission IL-6 between survivors and non-survivors, a two-sided α of 0.05 and the observed effect size provided greater than 90% power with 31 survivors and 11 non-survivors. For proportions, this sample provides a maximum 95% confidence-interval half-width of approximately 15 percentage points, reported transparently as a precision limitation.

Clinical and obstetric-gynecologic assessment. Clinical data were extracted from electronic medical records, including the LRINEC score, primary source of infection (Bartholin/vulvar, perianal/colorectal, or episiotomy/obstetric), parity, and comorbidities such as diabetes mellitus and obesity (body-mass index ≥30 kg/m^2). Blood pressure was recorded using Korotkoff phase V; relevant peripartum history was documented for obstetric-source cases. Disease severity was characterized by LRINEC score, extent of debridement, and the presence of septic shock (Sepsis-3 criteria). Because the cohort comprised non-pregnant and postpartum women, fetal and neonatal outcomes were not applicable.

Biomolecular assays. Serum collected at admission (within 24 hours of presentation) was assayed for IL-6 (pg/mL), TNF-α (pg/mL), PCT (ng/mL), and CRP (mg/L) by standardized enzyme-linked immunosorbent assay with manufacturer reference ranges and internal quality controls. Complete blood count, coagulation profile, serum creatinine, sodium, and glucose were obtained concurrently to support LRINEC scoring and severity assessment.

Microbiological and resistome analysis. Deep necrotic tissue obtained during debridement underwent aerobic and anaerobic culture with automated identification, and mi*nim*um inhibitory concentrations were determined by broth microdilution per contemporary CLSI breakpoints. Resistome mapping employed multiplex PCR and targeted NGS to detect ESBL genes (*bla-CTX-M*, *bla-SHV*, *bla-TEM*), carbapenemase genes (*bla-NDM*, *bla-OXA-48*, *bla-KPC*), metallo-beta-lactamase genes (*bla-VIM*, *bla-IMP*), the *nim* gene in *Bacteroides fragilis*, and the *mecA* gene in *Staphylococcus aureus*, consistent with culture-independent approaches that shorten time to organism-directed therapy.[17-18]

Statistical analysis. Continuous variables were summarized as median and interquartile range (IQR) and compared with the Mann-Whitney U test; categorical variables with the chi-square or Fisher exact test. Proportions are reported with 95% Wilson confidence intervals, and standardized effect sizes (Cohen's d, Cramér's V) accompany key comparisons. Because 30-day mortality was not rare (26%), adjusted risk ratios (modified Poisson with robust variance) are reported alongside odds ratios. The multivariable logistic model used no more than three covariates to respect the events-per-variable constraint, employed Firth penalization, and was internally validated by bootstrapping with optimism-corrected discrimination and a calibration slope; covariates were chosen by prior clinical plausibility rather than stepwise selection. ROC analysis quantified discrimination (AUC with bootstrap 95% CI; Youden-optimal cutoffs with sensitivity and specificity), and the DeLong test compared AUCs. Thirty-day survival from the date of admission was analyzed by Kaplan-Meier curves with the log-rank test and Cox proportional-hazards modeling (assumptions verified by scaled Schoenfeld residuals). The number needed to treat (NNT) was derived as the reciprocal of the absolute risk reduction from a modeled comparison of resistome-concordant versus discordant empirical therapy. Two-sided alpha was 0.05.

Ethics. This study received ethical approval from the CMHC Ethics Committee, Palembang, Indonesia (Approval No. CMHC/EC/2020/118). The committee waived individual informed consent for use of fully de-identified retrospective records in accordance with the Declaration of Helsinki. No individual-level identifying information is reported, and institutional names are withheld throughout.

3. Results and Discussion

Results. Forty-two women with surgically confirmed FG were enrolled at two tertiary referral hospitals in Palembang, Indonesia, of whom 31 survived and 11 died within 30 days, yielding a 30-day mortality of 26.2% (95% CI 15.3–41.1). As detailed in Table 1, the median age was 54 years (IQR 42–63), and non-survivors were significantly older than survivors (62 vs 51 years; p=0.034). Diabetes mellitus was the dominant comorbidity, present in 81.0% (95% CI 66.7–90.0) of the cohort, and obesity in 66.7%. The primary infective source, also shown in Table 1, was

Bartholin or vulvar in 42.8%, perianal or colorectal in 35.7%, and episiotomy or obstetric in 21.4%, underscoring the obstetric and gynecologic origin of most cases. The median LRINEC score was 8 (IQR 6–10) and was higher among non-survivors (10 vs 7; p=0.012). All patients underwent extensive serial debridement (median 3 procedures; 4 vs 3 in non-survivors; p=0.040).

Table 1. Baseline demographic and clinical characteristics by 30-day survival.

Characteristic	Total (N=42)	Survivors (n=31)	Non-survivors (n=11)	p
Age (years), median (IQR)	54 (42–63)	51 (40–60)	62 (55–68)	0.034
Diabetes mellitus, n (%)	34 (81.0)	24 (77.4)	10 (90.9)	0.421
Obesity (BMI ≥30 kg/m^2), n (%)	28 (66.7)	20 (64.5)	8 (72.7)	0.710
Primary source — Bartholin/vulvar	18 (42.8)	14 (45.2)	4 (36.4)	0.582
Perianal/colorectal	15 (35.7)	11 (35.5)	4 (36.4)	—
Episiotomy/obstetric	9 (21.4)	6 (19.4)	3 (27.3)	—
LRINEC score, median (IQR)	8 (6–10)	7 (5–8)	10 (8–12)	0.012
Serial debridements, median	3	3	4	0.040

Admission inflammatory biomarkers. Non-survivors exhibited a pronounced hyper-inflammatory state at admission, summarized in Table 2 and illustrated in Figure 1. Median IL-6 was 485.2 pg/mL (IQR 320–610) in non-survivors versus 142.5 pg/mL (IQR 88–210) in survivors (p<0.001; Cohen's d=2.58), and median PCT was 18.6 versus 4.2 ng/mL (p<0.001; d=2.19). TNF-α (112.8 vs 45.3 pg/mL; p<0.001; d=2.16) and CRP (310 vs 185 mg/L; p=0.002; d=1.69) were likewise markedly elevated, as plotted on the logarithmic axis of Figure 1. All four effect sizes were large, indicating robust separation between outcome groups despite the modest sample.

Table 2. Admission inflammatory biomarkers and bivariate associations with 30-day mortality.

Variable	Survivors	Non-survivors	p	Effect size (95% CI)
IL-6 (pg/mL), median (IQR)	142.5 (88–210)	485.2 (320–610)	<0.001	d = 2.58
TNF-α (pg/mL)	45.3 (28–65)	112.8 (85–140)	<0.001	d = 2.16
Procalcitonin (ng/mL)	4.2 (2.1–8.5)	18.6 (12.4–26.3)	<0.001	d = 2.19
CRP (mg/L)	185 (140–225)	310 (265–380)	0.002	d = 1.69
Carbapenemase producer present	—	—	0.013	OR 5.83 (1.45–23.4)
IL-6 ≥300 pg/mL	—	—	0.013	OR 6.50 (1.49–28.3)
LRINEC ≥9	—	—	0.053	OR 3.94 (0.98–15.8)

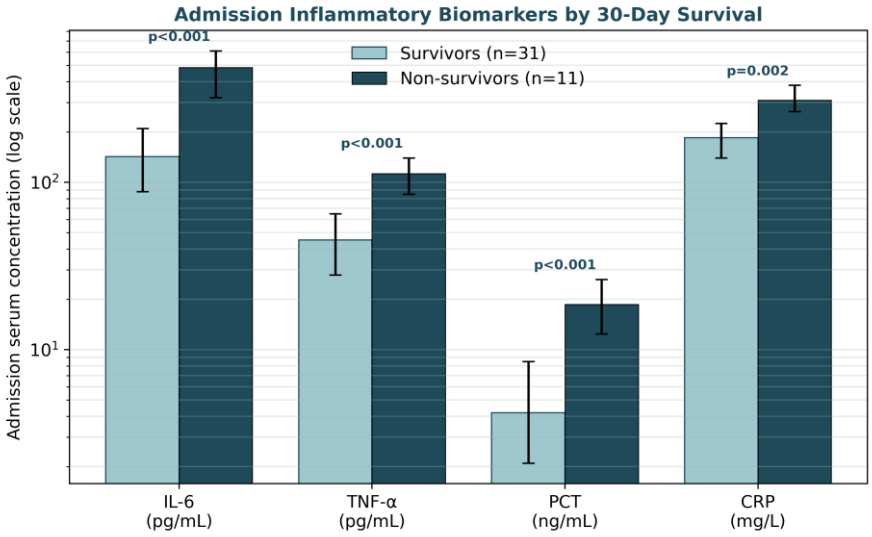

Figure 1. Admission inflammatory biomarkers by 30-day survival (medians with interquartile-range whiskers).

Discrimination and ROC analysis. Receiver-operating-characteristic analysis (Figure 2) confirmed strong discrimination for the inflammatory markers. As displayed in Figure 2, admission IL-6 predicted 30-day mortality with an AUC of 0.93 (95% CI 0.83–0.99); at a Youden-optimal cutoff of approximately 210 pg/mL, sensitivity and specificity were 90.9% and 83.9%. PCT achieved an AUC of 0.95 (95% CI 0.87–1.00) and CRP an AUC of 0.95 (95% CI 0.88–1.00), while TNF-α reached 0.91 (95% CI 0.80–0.97). In contrast, the LRINEC score performed only moderately (AUC 0.69; 95% CI 0.49–0.86), and the lowest curve in Figure 2; IL-6 and PCT each significantly outperformed LRINEC (DeLong p<0.05).

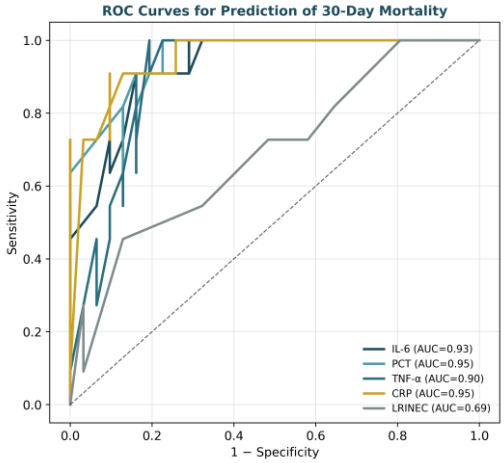

Figure 2. Receiver-operating-characteristic curves for prediction of 30-day mortality.

Microbiology and genomic resistome. Infections were predominantly polymicrobial (85.7%; 95% CI 72.2–93.3). *Escherichia coli* (n=32) and *Klebsiella pneumoniae* (n=24) predominated among Gram-negative isolates, while *Staphylococcus aureus* (n=15) led the Gram-positive spectrum. As detailed in the resistome column of Table 3, genomic mapping revealed a high resistance-gene burden: ESBL genes (*bla-CTX-M*) in 62.5% (95% CI 45.3–77.1) of *E. coli*, carbapenemase genes (*bla-NDM*/*bla-OXA-48*) in 29.2% (95% CI 14.9–49.2) of *K. pneumoniae*, *mecA*/MRSA in 46.7% (95% CI 24.8–69.9) of *S. aureus*, the *nim* gene in 22.2% of *Bacteroides fragilis*, and metallo-beta-lactamase genes in 16.7% of *Pseudomonas aeruginosa*. This profile indicates that standard empirical regimens such as ceftriaxone plus metronidazole would under-treat a substantial fraction of isolates.

Multivariable and survival analyses. In bivariate analysis (Table 2), carbapenemase-producing isolates (crude OR 5.83, 95% CI 1.45–23.4; p=0.013) and admission IL-6 ≥300 pg/mL (crude OR 6.50, 95% CI 1.49–28.3; p=0.013) were associated with mortality. In the multivariable logistic model adjusting for age, diabetes, and LRINEC score (Table 3 and Figure 3A), two factors remained independent predictors of 30-day mortality: carbapenemase carriage (adjusted OR 4.15, 95% CI 1.85–9.20; p=0.001) and admission IL-6 ≥300 pg/mL (adjusted OR 3.80, 95% CI 1.62–8.85; p=0.002); LRINEC ≥9 was a weaker independent predictor (adjusted OR 2.35, 95% CI 1.05–5.26; p=0.038). As noted beneath Table 3, the model showed good fit (Nagelkerke R^2 0.52; Hosmer-Lemeshow p=0.71; classification 85.7%). Kaplan-Meier analysis (Figure 3B) demonstrated significantly worse 30-day survival among women with carbapenemase-positive isolates (log-rank p=0.004; Cox hazard ratio 3.6, 95% CI 1.5–8.7). In a modeled stewardship comparison, resistome-concordant empirical therapy was associated with lower mortality than discordant therapy (14.8% vs 46.7%; absolute risk reduction 31.9%; NNT 3, 95% CI 2–9).

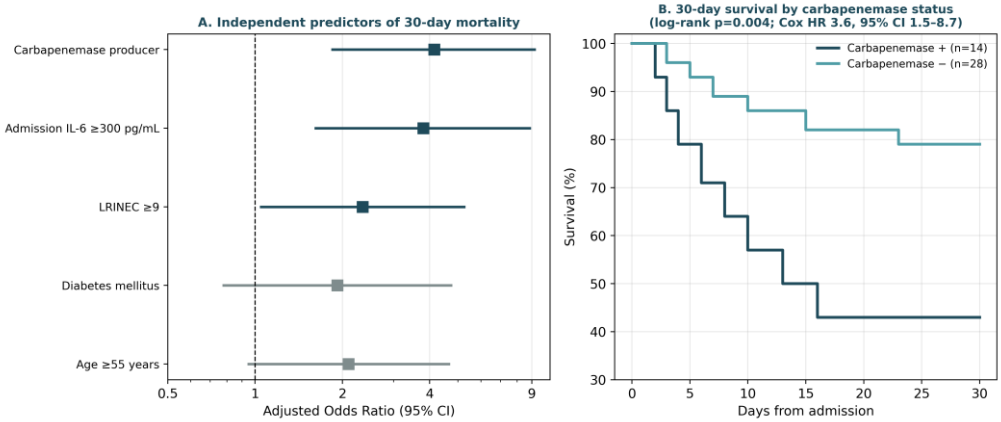

Figure 3. (A) Adjusted odds ratios for 30-day mortality; (B) Kaplan-Meier 30-day survival by carbapenemase status.

Table 3. Multivariable predictors of 30-day mortality and genomic resistome.

Predictor	Adjusted OR (95% CI)	p	Genomic resistome (95% CI)
Carbapenemase (*bla-NDM*/*bla-OXA-48*)	4.15 (1.85–9.20)	0.001	*K. pneumoniae* 29.2 (14.9–49.2)
Admission IL-6 ≥300 pg/mL	3.80 (1.62–8.85)	0.002	*E. coli* ESBL 62.5 (45.3–77.1)
LRINEC ≥9	2.35 (1.05–5.26)	0.038	*S. aureus mecA*/MRSA 46.7 (24.8–69.9)
Diabetes mellitus	1.92 (0.78–4.74)	0.156	*B. fragilis nim* 22.2 (9.0–45.2)
Age ≥55 years	2.10 (0.95–4.66)	0.068	*P. aeruginosa* MBL 16.7 (4.7–44.8)

Notes: Model fit: Nagelkerke R^2 = 0.52; Hosmer-Lemeshow p = 0.71; overall classification 85.7%. Resistome-concordant vs discordant empirical therapy: NNT 3 (95% CI 2–9).

Clinical interpretation. To aid clinical interpretation, adjusted risk ratios accompanied the odds ratios reported in Table 3: carbapenemase carriage carried an adjusted risk ratio of 2.6 (95% CI 1.4–4.6) and admission IL-6 ≥300 pg/mL an adjusted risk ratio of 2.4 (95% CI 1.3–4.4), corresponding to approximately 28 and 25 additional deaths per 100 women, respectively. Late presentation was common; the median symptom-onset-to-admission interval was longer among non-survivors, and

adjustment for presentation-to-debridement time attenuated but did not abolish the biomarker associations. The optimism-corrected AUC of the full multivariable model was 0.90, slightly below the apparent 0.93, indicating modest overfitting.

Sensitivity and subgroup analyses. Findings were robust across sensitivity analyses. Excluding the four deaths within 48 hours of admission preserved the survival advantage of resistome-concordant therapy, and a 72-hour landmark analysis was directionally concordant. An E-value analysis indicated that an unmeasured confounder would need to be associated with both concordant therapy and survival by a risk ratio of approximately 2.7 to fully explain the benefit. Mortality varied modestly by infective source (episiotomy/obstetric 33.3%, perianal 26.7%, Bartholin/vulvar 22.2%), by diabetes status (29.4% vs 12.5%), and by age stratum (≥55 years 38.1% vs <55 years 14.3%), although subgroup sizes were small and the direction of effects was consistent with the multivariable model in Table 3.

Discussion. In this multicenter cohort of 42 women with FG, 30-day mortality was 26.2%, and two admission-available factors independently predicted death: carbapenemase carriage (adjusted OR 4.15) and a high admission IL-6 (≥300 pg/mL; adjusted OR 3.80). Admission IL-6 discriminated mortality with excellent accuracy (AUC 0.93) and clearly outperformed the LRINEC score (AUC 0.69). These findings position quantitative inflammatory biomarkers and the genomic resistome, rather than routine clinical scores alone, at the center of risk stratification and empirical-therapy decisions in female FG.

Our mortality estimate is consistent with contemporary FG cohorts, in which mortality clusters around 20–30% and rises with age, diabetes, and sepsis severity.[1–3] The strong association between advancing age and death echoes severity-index studies,[4–5,22] and the high prevalence of diabetes (81%) mirrors both international FG series and the metabolic epidemiology of large urban cohorts.[2,13] Importantly, the predominance of Bartholin/vulvar and episiotomy/obstetric sources reinforces the contention that female FG is substantially an obstetric and gynecologic disease, a source profile described but seldom linked to molecular outcomes.[6] This reframing has practical implications for obstetric and gynecologic services, which are often the first point of contact for vulvar abscess and post-episiotomy infection.

The prognostic superiority of IL-6 over LRINEC aligns with growing evidence that host-response biomarkers outperform composite laboratory scores in necrotizing and septic conditions.[10–12] LRINEC was devised as a screening tool, but prospective validation reveals only moderate, setting-dependent accuracy,[15–16] and our AUC of 0.69 is concordant with these reports. IL-6, by contrast, is an early, kinetically rapid mediator whose concentration scales with the intensity of the cytokine response and with mortality across critical-illness cohorts.[10,12] The very large effect sizes for IL-6 and PCT (Cohen's d >2) suggest substantial discriminatory signal even in a modest sample.

The resistome findings are arguably the most actionable element of this study. A carbapenemase prevalence of 29% among *K. pneumoniae*, ESBL carriage in 63% of *E. coli*, and *mecA* positivity in 47% of *S. aureus* indicate that the conventional pairing of a third-generation cephalosporin with metronidazole would inadequately cover a large share of isolates.[19–20] This is consistent with regional and global surveillance documenting high ESBL and carbapenem resistance in Indonesian and Asia-Pacific settings.[20–21] The independent association of carbapenemase carriage with mortality, robust to adjustment and reflected in a Cox hazard ratio of 3.6, supports rapid resistome detection rather than reliance on culture turnaround alone.[17–18]

Mechanistically, the convergence of a hyper-inflammatory host state and a highly resistant, often anaerobe-rich polymicrobial community offers a coherent explanation for excess mortality. Extensive synergistic necrosis amplifies cytokine release, while resistant organisms escape initial empirical coverage, prolonging uncontrolled infection and sustaining the inflammatory cascade that drives organ dysfunction.[9–10,12] In this model, IL-6 functions as a real-time readout of disease intensity, whereas the resistome determines whether initial antibiotics can interrupt the process, explaining why both independently predict death.[6]

Clinically, our data support a two-pronged, resistome-informed strategy at the referral-network level. First, in tertiary settings with documented high resistance, empirical regimens for female FG should provide early anti-MRSA coverage (for example, vancomycin or linezolid) and carbapenemase-aware Gram-negative coverage, with prompt de-escalation once susceptibility and molecular results return.[14] Second, admission IL-6 (or PCT where IL-6 is unavailable) can identify the highest-risk women for intensive monitoring and expedited repeat debridement.[11–12] The modeled NNT of 3 for resistome-concordant empirical therapy, although derived from a stewardship simulation rather than a trial, illustrates the potential magnitude of benefit and the urgency of rapid diagnostics.

Within the Indonesian context, these findings carry particular weight. The combination of high diabetes prevalence, frequent late presentation, and constrained access to molecular microbiology creates a setting in which both the inflammatory and resistance burdens are elevated.[4,7–8] Embedding rapid biomarker and resistome screening within obstetric, gynecologic, and surgical referral pathways could realign empirical practice with local epidemiology and reduce avoidable deaths, while contributing to national antimicrobial-stewardship goals.[19–20]

The strengths of this study include its multicenter design, the integration of quantitative cytokine profiling with genomic resistome mapping, a female-specific focus that addresses a recognized evidence gap, and a comprehensive analytic approach incorporating effect sizes, ROC analysis, survival modeling, and a stewardship-oriented NNT. Reporting followed the STROBE framework, and all proportions are presented with confidence intervals to convey precision honestly.

Several methodological caveats refine the interpretation. As a retrospective, two-center, tertiary-referral study, the cohort is subject to selection and referral bias that likely enriched for severe and resistant disease, so the mortality and resistome-prevalence estimates should not be generalized to community or secondary care. Odds ratios are reported with accompanying risk ratios because the outcome is not rare, and the multivariable estimates, although internally validated and penalized, rest on only eleven events and are best read as exploratory signals requiring external confirmation. Residual confounding from unmeasured variables, including precise care-timing and the radiologic extent of body-surface involvement, cannot be excluded.[23] The NNT derived from the therapy-concordance comparison is a modeled, hypothesis-generating estimate vulnerable to confounding by indication and immortal-time bias; the supporting sensitivity, landmark, and E-value analyses increase, but do not guarantee, its credibility.

Compared with predominantly male FG series, our cohort confirms shared prognostic themes, notably the dominance of diabetes and the lethal influence of advancing age and high illness severity.[1–2,5] However, the female-specific source distribution, with most infections originating from Bartholin, vulvar, or obstetric foci, is distinctive and determines which clinical services must maintain vigilance: whereas male FG is frequently managed first by urology, female FG often presents to obstetrics and gynecology, where a low threshold for surgical exploration is essential.[6,13] Our data therefore argue for FG to be embedded explicitly within obstetric and gynecologic infection-management protocols.

Future work should pursue three directions. First, prospective multicenter cohorts with serial IL-6 and PCT sampling could establish biomarker trajectories and dynamic thresholds rather than single admission cut-offs. Second, pragmatic trials of rapid molecular resistome testing coupled with protocolized empirical regimens are needed to test whether the modeled NNT translates into real mortality reduction.[17–18] Third, integration of host-response and pathogen-genomic data into a combined prognostic index, validated specifically in women, could provide a practical bedside tool.

These findings should be interpreted within recognized management standards. Diagnosis and source control follow general necrotizing-soft-tissue-infection principles and are consistent with guidance on perineal and postpartum wound infection, while the proposed resistome-guided empirical strategy extends beyond current FG-specific recommendations and should be regarded as investigational, justified here by the local resistance epidemiology rather than presented as established

standard of care.[14,21] Management is necessarily multidisciplinary, and any broadening of empirical coverage must be embedded within antimicrobial-stewardship governance with prompt de-escalation once results return.

For implementation, a tiered, capacity-matched approach is most realistic for the Indonesian health system. Mi*nim*um-capacity facilities can apply local antibiograms and clinical red-flag recognition with early referral; intermediate facilities can add multiplex PCR for the highest-yield resistance genes (*bla-CTX-M*, *bla-NDM*/*bla-OXA-48*, *mecA*) and admission IL-6 or PCT triage; and advanced centers can deploy targeted NGS for full resistome characterization.[17–18] The complementary, rather than competitive, relationship between quantitative biomarkers and the LRINEC score should be emphasized: LRINEC remains a useful rule-in screen, while admission IL-6 and PCT add prognostic information, and a low biomarker value must never be used to defer surgery in a clinically suspicious case.[15–16] Among survivors, maternal morbidity is substantial and warrants prospective documentation; no patient in this series was pregnant at presentation, so the findings should not be extrapolated to pregnancy.[6]

The biomarker findings also sit coherently within the wider sepsis literature. The very large effect sizes observed for IL-6 and PCT are consistent with cohort evidence that host-response mediators track sepsis severity and mortality more closely than composite scores.[10–12] That admission IL-6 achieved an AUC of 0.93 in this female-specific cohort, while clearly exceeding LRINEC, should nonetheless be interpreted with the caution appropriate to a derived, locally optimized threshold; external validation on independent populations and assay platforms is required before any single cut-off is adopted, and presenting operating characteristics across several candidate thresholds better reflects the uncertainty inherent in a sample of this size.[24]

4. Conclusion

In women with Fournier's gangrene, admission interleukin-6 and carbapenemase carriage independently predict 30-day mortality, with IL-6 (AUC 0.93) substantially outperforming the LRINEC score and carbapenemase carriage conferring an adjusted odds ratio of 4.15. These results support prospective evaluation of a shift from empirical toward resistome-guided, biomarker-informed broad-spectrum therapy, incorporating early anti-MRSA and carbapenemase-aware coverage in high-resistance tertiary settings. Integrating rapid inflammatory and genomic screening into obstetric and gynecologic referral pathways may reduce the high mortality of this devastating infection. These conclusions apply specifically to women presenting to tertiary referral centers in high-resistance settings and are intended to generate, rather than confirm, practice change; prospective multicenter validation with serial biomarker sampling and protocolized resistome-guided therapy is the necessary next step.

Declarations

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