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Diagnostic Value of Routine Biomarkers in Predicting Septicaemia in Hospitalised Patients: A Cross-sectional Study

Microbiology Section

BHAGWATI CHUNDAWAT[1], SAKSHEE GUPTA[2], ALKA MEENA[3]

ABSTRACT

Introduction: Sepsis is a potentially fatal condition that leads to alterations in coagulation, immunosuppression, and multiorgan failure. Predicting the risk of septicaemia before the onset of organ dysfunction poses a challenge. Prompt diagnosis, coupled with triaged management, is crucial in determining disease outcomes.

Aim: To assess the role of routinely employed biomarkers in the early identification of septicaemia in patients.

Materials and Methods: A cross-sectional study was conducted on 564 blood samples from Jaipur National University Institute of Medical Sciences and Research Centre (JNUIMSRC) in Jaipur, Rajasthan, India, over a period of six months (July 2019-December 2019). Blood culture, identification, and antimicrobial sensitivity testing were performed for all the samples following the Clinical and Laboratory Standards Institute (CLSI- M100) guidelines. Standard septic markers, such as Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Serum Glutamic Pyruvic Transaminase (SGPT), Serum Glutamic Oxaloacetic Transaminase (SGOT), serum urea, serum creatinine, Haemoglobin (Hb), and Total Lymphocyte Count (TLC), were studied. The culture-positive patients were compared with a negative control group. The t-test and logistic regression were used for analysis.

Results: Out of 564 patients suspected of sepsis, 135 (23.94%) were culture positive, with a male-to-female ratio of 1.41. No significant differences were found in septic markers {TLC (p-value=0.261), ESR (p-value=0.186), SGPT (p-value=0.336), SGOT (p-value=0.264), Hb (p-value=0.179), serum urea (p-value=0.350), and serum creatinine (p-value=0.155)} between the culture-positive group (135/564, 23.93%) and the culture-negative group (429/564, 76.06%), except for CRP (p-value=0.006). The results of logistic regression also showed that CRP was a significant predictor of septicaemia (p-value=0.009). Amikacin, doxycycline, and piperacillin-tazobactam were found to be sensitive.

Conclusion: Currently used blood markers do not provide sufficient evidence for the prediction of septicaemia, although CRP may be preliminarily useful. There is an urgent need to combine them with novel markers for the early detection of septicaemia.

Keywords: Antibiogram, Blood culture, C-reactive protein, Routine blood markers, Septicaemia

INTRODUCTION

Sepsis is a leading cause of mortality, ranging from 30-63% [1], increased hospital stay, and readmissions worldwide, with 18 million new sepsis cases reported each year [2]. "Sepsis" involves multiorgan dysfunction caused by a deregulated host response to infection, whereas "septic shock" is associated with circulatory and cellular/metabolic dysfunction, as per the consensus definition of Sepsis-3 [3]. Since a high proportion of critically ill patients present with Systemic Inflammatory Response Syndrome (SIRS), clinicians are faced with the challenge of accurately distinguishing between both.

Laboratory biomarkers help physicians monitor therapeutic decisions and plan treatment accordingly [4]. More than 100 sepsis biomarkers have been proposed and documented in the literature. However, they have limitations in distinguishing sepsis from other inflammatory conditions and predicting outcomes. Hence, no ideal marker has been found to date, owing to the complex pathobiology of the disease. According to the Surviving Sepsis Guidelines 2021, sepsis biomarkers were not found to have a definitive role in clinical evaluation [5].

International guidelines for the management of sepsis have given a weak recommendation regarding the use of serum lactate as an adjunctive test to pretest sepsis in suspected sepsis cases [3]. CRP and ESR are markers of inflammation that poorly correlate with clinical measures of disease severity [6]. Many authors have studied that bacteraemia may be predicted by an increase in Total Leukocyte Count (TLC) with fever [7], D-dimer [8], lactate, Prothrombin Time/International Normalised Ratio (PT/INR) [9], eosinophil count [10], interleukin-6 and 8 (IL-6 and IL-8) [11], and Procalcitonin (PCT) [11]. PCT has been extensively studied and incorporated into practice. Pro-vasopressin (pro-AVP)/proadrenomedullin (ProADM) [12], resistin level [13], biomarkers of complement proteins, activated neutrophils, and monocytes can also complement diagnosis. According to Camacho CH and Losa J, novel markers of bloodstream infections like soluble Triggering Receptor on Myeloid cells-1 (sTREM-1), soluble urokinase-type plasminogen receptor (suPAR), proadrenomedullin (ProADM), and presepsin appear promising because of acceptable sensitivity and specificity [14]. It is the need of the hour to identify novel sepsis biomarkers conducive to the respective laboratory set-up of each hospital and incorporate them into clinical practice [15,16]. The present study was undertaken to assess the utility of currently employed septic markers (CRP, ESR, TLC, SGOT, SGPT, Hb, serum urea, and creatinine) in predicting the risk of septicaemia in hospitalised patients.

The antibiotic susceptibility pattern of the isolates from Intensive Care Unit (ICU) and wards is helpful to commence empirical treatment before laboratory results are available. Commonly isolated organisms from blood culture, such as *Acinetobacter* spp., *Enterobacter* spp., *Pseudomonas* spp., *Staphylococcus* spp., Coagulase-negative *Staphylococcus*, etc., may present with plasmid-mediated or chromosomally acquired resistance [17]. Hospitals are now emphasising the preparation of unit-wise antibiograms for effective patient management. Hence, the sensitivity pattern of the culture isolates was analysed for the study population. Due to the lack of advanced infrastructure in resource-limited settings (primary/community healthcare centres and remote areas), prompt administration of empirical therapy becomes challenging [17]. Literature probing into the role of conventional biomarkers in the early

prediction of sepsis is also scarce in developing countries. Hence, the novelty of present study lies in the assessment of the utility of currently available markers in ICU and hospital settings, in culture-positive/negative controls, and the assessment of the antibiogram. The aim of the study was to assess the role of routinely employed biomarkers in the early identification of septicaemia in patients.

MATERIALS AND METHODS

A cross-sectional study was conducted between July 2019 and December 2019 (six months) to study the conventional biomarkers of sepsis, such as TLC, Hb levels, ESR, SGOT, SGPT, CRP, serum urea, and serum creatinine, in the Department of Microbiology, JNUIMSRC, Jaipur, Rajasthan, India. Consent forms were filled out by the patients participating in the study after approval from the ethical and research committee of the institution (JNUIMSRC/IEC/2020/192).

Inclusion criteria: All significant bacterial isolates obtained by blood culture were included in the study.

Exclusion criteria: Contaminants/commensals, yeasts, and anaerobes were excluded from the study.

Sample size: The calculation of the sample size was done by the Department of Statistics based on data on the prevalence of septicaemia in resource-limited settings [1].

$$n=\frac{Z^2p(1-p)}{d^2}$$

Where n is the sample size, Z is the level of confidence taken as 1.96, P prevalence is 6.0% (Chatterjee S et al.), and d is the precision taken as ±5% (95% confidence interval). Blood samples were procured from 564 patients with signs and symptoms of septicaemia reporting at the hospital. Sepsis was diagnosed by the consultant physician based on the clinical condition of the patient and laboratory evidence.

For blood culture, one set of bottles (paired aerobic and anaerobic bottles, each containing 10 mL of blood) was received by the laboratory after bedside sample collection from the hospital. Cultures were incubated at 37°C in an automated BACTEC blood culture system (Becton Dickinson and Company, Sparks, MD, USA). Bottles were monitored for five days and subcultured on MacConkey agar, blood agar, and chocolate agar if flagged positive by the instrument. The rest of the bottles were discarded on the 6th day. A sample was categorised as "culture positive" when a pathogen was isolated and identified after subculture. The samples yielding clinically "insignificant" pathogens/negative by the blood culture instrument were considered "culture negative". Data of culture-positive patients were compared with the culture-negative control group.

Identification and antibiotic sensitivity were performed as per CLSI guidelines (M100), 30th edition [18]. Preliminary tests (catalase, coagulase, oxidase, hanging drop, etc.) and biochemical tests (Sulphur, Indole, Motility (SIM), Oxidation-Fermentation (OF), indole, citrate, urease, sugar fermentation tests, Methyl Red (MR), Voges-Proskauer (VP), etc.) were performed for the identification of gram-positive and gram negative isolates. Standard disks (Hi Media Labs) were used for antimicrobial sensitivity testing for gram-positive and gram negative bacterial isolates as per CLSI [18]. The following antibiotics were tested: Amikacin (AK) (30 µg), Amoxicillin/Clavulanic Acid (AMC) (30 µg), Azithromycin (AZM) (15 µg), cefepime (FEP) (30 µg), Ceftazidime (CAZ) (30 µg), Ceftriaxone (CRO) (30 µg), Cefuroxime (CXM) (30 µg), Ciprofloxacin (CIP) (5 µg), Clindamycin (DA) (2 µg), Colistin (C) (5 µg), Trimethoprim/Sulfamethoxazole (SXT) (25 µg), Doxycycline (DO) (30 µg), Erythromycin (E) (15 µg), Gentamicin (CN) (10 µg), Imipenem (IMI) (10 µg), Levofloxacin (LEV) (5 µg), Linezolid (LZD) (30 µg), Meropenem (MEM) (10 µg), Moxifloxacin (MX) (10 µg), Piperacillin/Tazobactam (TZP) (110 µg), Teicoplanin (TEI) (10 µg), Tobramycin (TOB) (10 µg), and Vancomycin (VA) (30 µg).

E. coli (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), and *Staphylococcus aureus* (ATCC 29213) were used as reference strains following CLSI M100 guidelines.

Blood samples were analysed for routinely used septic markers, including ESR, CRP, SGPT, SGOT, serum urea, serum creatinine, haemoglobin, and TLC [19]. Serum urea, creatinine, SGOT, and SGPT were analysed using an automated RX Imola biochemical analyser (RANDOX Laboratories Ltd.). TLC was performed using the Yumizen H550 automated system (Horiba ABX SAS), and ESR was measured using the Westergren tube method, with values >25 mm/h considered abnormal [6]. CRP was determined using a latex agglutination card test [19].

STATISTICAL ANALYSIS

The data were presented as median values with a 95% confidence interval due to the skewed distribution of most variables. Univariate analysis, using Analysis of Variance (ANOVA), was performed to compare the conventional septic markers used in the present study and derive Odds Ratios (OR). A p-value ≤0.01 was considered significant. All analyses were performed using Statistical Package for Social Sciences (SPSS) version 21.0 (SPSS, Chicago, IL, USA).

RESULTS

Out of the total 564 samples, 135/564 (23.94%) were culture-positive, with a mean age of 42.5±15 years and a male-to-female ratio of 1.41. Among the 135 culture-positive patients, 56/135 (41.48%) were females, most 48.21% (27/56) of which were in their reproductive age group (21-50 years), and 49/135 (36.29%) were elderly patients (age 51-75 years).

On comparative analysis, all septic markers had insignificant p-values, such as TLC (p-value=0.261), ESR (p-value=0.186), SGPT (p-value=0.336), SGOT (p-value=0.264), haemoglobin (p-value=0.179), serum urea (p-value=0.350), and serum creatinine (p-value=0.155), except for CRP (p-value=0.006), which was significant. The CRP levels were higher in culture-positive patients compared to the culture-negative control group [Table/Fig-1].

Markers	Number of culture positive patients (n=135, mean)	Number of culture negative controls (n=429, mean)	p-value
Age (years)	45±22	40±23	0.233
M:F Ratio	1.41	1.53	0.191
TLC (cells/µL)	9.2±7.74	12.18±3.31	0.261
ESR (mm/hr)	35±28.61	32.71±26.42	0.186
CRP (mg/dL)	11.47±16.72	10.54±11.23	0.006
SGOT (units/L)	25.66±22.8	23.32±13.76	0.264
SGPT (units/L)	25.95±11.43	18.64±13.66	0.336
Hb (g/dL)	9.46±2.32	10.71±3.01	0.179
Serum urea (mg/dL)	46.29±19.43	35.5±20.01	0.350
Creatinine (mg/dL)	1.6±0.92	1.71±1.00	0.155

[Table/Fig-1]: Comparative analysis of characteristics in culture positive and culture negative control organisms.
**t-test, p ≤0.01- Significant; *TLC: Total lymphocyte count markers; ESR: Erythrocyte sedimentation rate); Hb: haemoglobin; SGOT: Serum glutamic oxaloacetic transaminase); SGPT: Serum glutamic pyruvic transaminase; and CRP: C-reactive protein

The culture positivity rate was comparable between the wards and ICUs with 77/319 (24.13%) and 58/245 (23.67%) positive cultures (p-value=0.31) respectively [Table/Fig-2].

No. of patients	Wards	ICU	p-value
Total	319	245	p=0.31
Culture positive	77	58	
	24.13%	23.67%	

[Table/Fig-2]: Comparison of culture positivity from wards and ICU.
*t-test, p ≤0.01- Significant

The results of the logistic regression analysis showed that CRP was significantly associated with prediction of septicaemia among the study population compared to other biomarkers such as TLC, ESR, SGOT, SGPT, Hb, serum urea, and creatinine (OR=1.134, p-value <0.01) [Table/Fig-3].

Variables	Univariate analysis (ANOVA)		
	OR	CI	p-value
TLC	0.985	0.843-1.083	0.832
ESR	1.057	1.014-1.058	0.958
CRP	1.134	1.102-1.105	0.009
SGOT	0.856	0.915-1.007	0.799
SGPT	0.937	0.847-1.027	0.848
Hb	1.000	1.000-1.000	0.943
Serum urea	0.898	0.995-1.003	0.665
Creatinine	0.993	0.999-1.005	0.763

[Table/Fig-3]: Logistic regression analysis predicting septicaemia in patients.
**Analysis of variance (ANNOVA), p≤0.01-Significant; *TLC: Total lymphocyte count markers; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; Hb: Haemoglobin

Upon culture, 76/135 (56.30%) isolates were found to be gram-positive, and 59/135 (43.70%) were gram negative. Among gram-positive cocci, the maximum number of isolates were Methicillin-Resistant *Staphylococcus aureus* (MRSA) (32/135, 23.70%), followed by Coagulase-Negative Staphylococci (CONS) (30/135, 22.22%), including 6/30 (20%) methicillin-sensitive and 24/30 (80%) methicillin-resistant strains. Enterococci accounted for 8/135 (5.9%) of isolates, and Methicillin-Sensitive *Staphylococcus aureus* (MSSA) accounted for 6/135 (4.44%) of isolates. Among gram negative organisms, *Acinetobacter* spp. accounted for 18/135 (13.33%) of isolates, followed by *Pseudomonas* spp. and *Escherichia coli* with 14/135 (10.37%) each, *Enterobacter* spp. with 5/135 (3.7%), *Klebsiella* spp. and *Shigella* spp. with 4/135 (2.9%) each.

Antibiotic sensitivity testing revealed that more than 67% of strains were sensitive to amikacin, >40% were sensitive to doxycycline, and >53% were sensitive to piperacillin-tazobactam. 75-100% of gram negative bacteria were found to be sensitive to colistin. None of the strains were found to be resistant to vancomycin and linezolid [Table/Fig-4]. Out of the 564 patients suspected of sepsis, 429 (76.06%) tested negative for blood culture.

DISCUSSION

The diagnosis of sepsis is associated with a high rate of in-hospital mortality (27.6%) and multidrug resistance [20]. A higher percentage of males, 79/135 (58.52%), in the present study was consistent with a study from the US [21], which suggested that the incidence of bloodstream infections increases with age and is significantly higher in males. Septicaemia was found to be more frequent in young females of reproductive age, as the immunological and cardiovascular adaptations during pregnancy might impair their ability to respond to infection [22].

The culture positivity rates were comparable between the wards {77/319 (24.13%)} and the ICUs {58/245 (23.67%)} (p-value=0.31). Studies [23] have shown that the ICUs and emergency departments had significantly higher positivity rates compared to general wards {11.2% versus 5.7% (p-value <0.001)}. Since ICUs and wards are prone to infections, it is relevant to study septic markers, antibiograms, and other parameters of hospital-acquired infections in both settings.

Blood culture and antimicrobial sensitivity testing are recommended prior to deciding on antimicrobial therapy according to the Surviving Sepsis campaign's international sepsis guidelines [24]. Therefore, blood culture is the cornerstone of antibiotic stewardship programs [25]. Resource-limited settings face additional challenges, such as low recovery rates (30-40%) of pathogens from blood cultures. This can be due to various reasons, including discrepancies in sample collection, prior antibiotic administration, transportation delays, deviations from standard protocols in Standard Operating Procedures (SOPs) by untrained laboratory technicians, and lack of automation [26]. A recent study from the US has demonstrated that more than 89% of patients with signs and symptoms of sepsis were identified as culture-negative, similar to the findings of the present study. This emphasises the urgent need for novel biomarkers in the definitive diagnosis of sepsis in culture-negative samples [27].

A standard diagnostic tool is currently unavailable to predict bacteraemia at an early stage, as definitive culture results typically take atleast 48-72 hours. Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores are being used as predictors of fatal outcomes in critically ill patients. However, the roles of most clinical and laboratory biomarkers in the management of septic patients have not been well defined, as suggested by current literature [16].

In the present study, the levels of routinely used biomarkers in culture-positive samples were compared with a culture-negative group. It was found that CRP was significantly higher (p-value=0.006; p-value >0.05) in culture-positive patients. Similarly, Woodworth from the USA [28] reported that CRP accurately predicts sepsis and its severity in ICU patients. This finding was in line with other

Organisms isolated	N	Amikacin	Amoxyclav	Azithromycin	Cefepime	Ceftazidime	Ceftriaxone	Cefuroxime	Ciprofloxacin	Clindamycin	Colistin	Cotrimoxazole	Doxycycline	Erythromycin	Gentamicin	Imipenem	Levofloxacin	Linezolid	Meropenem	Moxifloxacin	Piperacillin\ tazobactum	Teicoplanin	Tobramycin	Vancomycin
MRSA	32	79	0	8	0	0	0	0	13	38	0	58	88	13	50	0	0	100	0	67	0	100	0	100
MSSA	6	100	0	57	0	0	0	0	43	86	0	43	100	57	100	0	0	100	0	71	0	100	0	100
MRCONS	24	96	0	16	0	0	0	0	40	44	0	32	92	12	88	0	0	100	0	68	0	100	0	100
MSCONS	6	100	0	38	0	0	0	0	63	88	0	63	100	38	86	0	0	100	0	75	0	100	0	100
Enterococci spp.	8	0	0	0	0	0	0	0	0	0	0	0	40	0	0	0	0	100	0	0	0	80	0	100
Acinetobacter spp.	18	0	0	0	27	33	33	0	60	0	80	53	73	0	47	60	53	0	40	0	53	0	40	0
Pseudomonas spp.	14	77	0	0	69	54	0	0	85	0	85	0	0	0	69	77	85	0	54	0	92	0	69	0
E. coli	14	67	36	0	18	9	18	9	27	0	82	27	55	0	64	64	27	0	64	0	64	0	0	0
Klebsiella spp.	4	100	50	0	25	25	25	25	50	0	100	50	50	0	75	75	0	0	75	0	75	0	0	0
Enterobacter spp.	5	70	63	0	25	39	27	0	53	0	100	50	66	0	47	57	79	0	60	0	74	0	0	0
Shigella spp.	4	75	75	0	0	0	0	0	75	0	75	25	75	0	75	100	25	0	75	0	75	0	0	0

[Table/Fig-4]: Antibiotic susceptibility pattern of the culture isolates.
*MRSA: Methicillin resistant *Staphylococcus aureus*; MRCONS: Methicillin resistant Coagulase negative Staphylococci; MSCONS: Methicillin sensitive Coagulase negative Staphylococci; MSSA: Methicillin sensitive *Staphylococcus aureus*
**Total culture positive patients=135; **Susceptibility of strains is described in percentages (%)

international [29] as well as Indian studies [19], although some authors have reported contradictory results [6]. However, this study did not find any significant differences (p-value >0.001) in the other routine biomarkers such as TLC, ESR, SGOT, SGPT, Hb, serum urea, and creatinine between the culture-positive and negative groups. According to a Japanese study, the mean WBC and ESR levels are significantly lower in culture-negative patients [30]. Due to the varying findings in different studies, the definitive association of biomarkers with septicaemia has not been established till date [16,31].

Univariate analysis suggested that routinely used biomarkers were not significant predictors of septicaemia, except for CRP (OR 1.134, p=0.009). The authors have discussed the role of biomarkers such as WBC (cut-off of 10,000/mm^3) [7], ESR, and CRP in predicting sepsis [29]. Hassan HR et al., studied that m-ESR was significantly associated with culture-proven sepsis [32], but a study from the USA [6] stated otherwise. Many have suggested that PCT is a more specific predictor of bacteraemia than CRP and ESR [33,34]. The serum PCT level rises and returns back to the normal range faster than CRP levels, making it a better biomarker for sepsis [34]. A recent report summarised that the combination of IL-6, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and INR may serve as a potential predictor of 28-day mortality in critically ill patients with sepsis or septic shock [9]. Factors such as lack of sensitivity specificity and the complexity of inflammatory processes limit the role of several currently used biomarkers in stratifying patients for treatment [31]. It was emphasised that currently targeted biomarkers provide insufficient evidence for treatment decisions. CRP can be helpful in combination with other clinical and laboratory parameters. Hence, positive cultures remain the gold standard for laboratory confirmation of sepsis.

All gram-positive isolates were sensitive to vancomycin (100%), followed by doxycycline (88%). Gram negative isolates were sensitive to Piperacillin/Tazobactam (PIT) (53-92%) and Gentamicin (GEN) (47-75%), similar to an Indian study (PIT-22-60%; GEN-25-100%) [35]. Levofloxacin provided comprehensive coverage for both gram-positive and gram negative bacteria, while penicillins and cephalosporins were ineffective [35]. In this study, 32/76 (42.10%) of GPCs were found to be MRSA, which was lower as compared to other studies [17]. The antibiotic sensitivity profile presented in this study raises an alarm for the decreased sensitivity to colistin among gram negative bacilli. The drug of choice may be amikacin, doxycycline, and piperacillin/tazobactam in susceptible isolates. Although resistance to vancomycin and linezolid was not encountered in this study, hospitals must strictly adhere to the antibiotic policy as Vancomycin-Resistant *Staphylococcus aureus* (VRSA), Vancomycin-Resistant Enterococci (VRE), and Linezolid-Resistant Enterococci (LRE) have been reported from hospitals [17]. Preparation of an antibiogram for each setting will be helpful in the administration of empirical antibiotics in critically ill patients and the prevention of multidrug resistance.

Limitation(s)

Although multiple biomarkers were considered in the present study, data for PCT, lactate, IL-6, and D-dimer couldn't be presented due to infrastructure limitations. In-depth studies with control groups, a significant study population, evaluation by appropriate statistical parameters, and validation are required. It is important to study the biological plausibility of biomarkers and alterations in their levels with the change in the pathobiology of infections.

The present study also emphasises that the diagnostic value of the existing biomarkers is not well established. Hence, rigorous efforts are needed to investigate the role of inflammatory markers in predicting sepsis, along with their combination with novel ones, rather than relying on a single biomarker for rapid diagnosis and prognosis.

CONCLUSION(S)

With the increasing cases of multidrug-resistant organisms, predicting septicaemia in the present scenario poses a challenge. The results indicate that elevated CRP may serve as an early indicator of sepsis. It is crucial to develop a standardised methodology to assess the usefulness of currently available and novel sepsis biomarkers, which can offer valuable and clinically relevant information.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Microbiology, JNUIMSRC, Jaipur, Rajasthan, India.
2. Assistant Professor, Department of Microbiology, JNUIMSRC, Jaipur, Rajasthan, India.
3. Assistant Professor, Department of Biochemistry, SMS Medical College, Jaipur, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sakshee Gupta,
Assistant Professor, Department of Microbiology, JNUIMSRC,
Jaipur-302017, Rajasthan, India.
E-mail: saksheegupta@gmail.com

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