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Cohort Study

Evaluation of plasma level of fibrinogen as a diagnostic criterion in acute appendicitis; cohort study

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ABSTRACT

Background: Acute appendicitis (AA) is the most common etiology of abdominal operation worldwide. Despite advances in diagnostic guidelines there are still missed patients. This study evaluates assumption of plasma fibrinogen as a diagnostic criterion in AA.

Method: All patients over 12 years who were referred to emergency department and underwent index open appendectomy were enrolled in this cohort study. Histopathologically confirmed positive reports for presence of AA were allocated in a group. Controls experienced open appendectomy although pathological study was negative for AA. In addition to registering demographic data, plasma sample was examined for fibrinogen, quantitative C-reactive protein (CRP), and complete blood count preoperatively. Variables were compared. The ROC curve was customized and correlation coefficient for study markers was measured.

Results: Total 168 patients were enrolled. From all, 96 (57.1%) had confirmed AA, histopathologically. Gender, age, race, and body mass index had no difference between study groups ($p > 0.05$). In almost all patients increasing in white cell counts and left cellular shift was observed ($p > 0.05$). However, plasma level of fibrinogen and CRP reached to 389.2 ± 229.99 mg/dL ($p = 0.001$) and 33.06 ± 16.29 mg/L ($p = 0.03$) respectively, which both were significantly elevated in positive AA. Analysis showed area under the curve of serum fibrinogen was 0.892 ($p < 0.001$) with a cut-off point of 272 mg/dL had about 66.7% (95% CI:58.2–73.3) sensitivity, 92.8% (95% CI: 89.5–96.1) specificity, and 0.698 ($p = 0.04$) correlation coefficient for diagnosis of AA.

Conclusion: Amounts of elevated serum fibrinogen could imply on the diagnosis of AA specifically when concordance of clinical findings except for increasing CRP is unremarkable.

1. Introduction

Acute appendicitis (AA) is a common pathological inflammatory condition of the appendix which makes surgery unavoidable in most cases. It seems in all age groups and genders commonly [1,2]. Diagnosis of the disease is confirmed by attributed valuable findings in patient's history, physical examination, and laboratory indexes. Both the Alvarado and the appendicitis inflammatory response scoring systems are of mostly applied diagnostic guidelines. Despite developments in the latters there are at least 12–23% of missed cases exist [2,3]. Because of the fact that postponing the diagnosis of AA may lead to severe complications specifically in high risk groups, for example in pregnancy, therefore it is important to decrease the incidence of missed cases. For the latter, finding laboratory indexes with more specificity could be a research approach. C-reactive protein (CRP) is of acute phase reactant laboratory factor which its sensitivity in diagnosis of AA is previously confirmed [4]. Following 6–12 h from inflammation initiation plasma level of CRP reaches to the point that is detectable [5]. Although the higher plasma level of measured CRP implied on the more severe inflammatory process and even complicated appendicitis, the marker was not enough whether sensitive or specific for early diagnosis of AA [6–8].

Plasma fibrinogen is of another confirmed acute phase reactant agent that is originally synthesized in hepatocytes and acts primarily in hemostasis, and inflammatory response following infective or traumatic

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stress. Pathologically, fibrinogen derivatives stimulate local fibroblasts and also polymorphonuclear (PMN) white cells to be demarginated and moved towards the stress area [9–12]. Since now, some previous studies have focused on measurement of plasma level of fibrinogen in patients who were assumed for the diagnosis of AA, although there was no general consensus obtained in results [13–15].

Considering the aforementioned data, this study was conducted to evaluate plasma level of fibrinogen as a diagnostic laboratory factor in patients who were hospitalized while AA was in differential diagnosis.

2. Materials and method

Current cohort study from the February 2019 to the October 2021 was conducted following approval of ethical committee in Kashan University of Medical Sciences which was encoded IR. KAUMS.MEDNT.REC.1399.212 and also registered as IRCT20191025616N3 which is available at www.irct.ir. From all participants signed written informed consent was obtained. All patients who were 12 years old or more and referred to emergency department of our hospital with AA in differential diagnosis were enrolled. Demographic data was obtained. Everyone with positive history of whether current pregnancy or breastfeeding, uncontrolled chronic diabetes mellitus or hypertension, end stage renal or liver diseases, previously confirmed inflammatory or autoimmune disorders, corticosteroid or immunosuppressive drugs consumption, and children were primarily excluded. Later, from all who underwent physical, laboratory, and radiologic examinations for confirmation of AA, patients who were not scheduled for index operation also were excluded. Additionally, pathological study containing positive report for appendicitis was the gold standard for the definition and definitive criteria for patient to be remained in analysis. Namely, patient with pathologically confirmed appendicitis was finally remained in the study. All patients experienced open appendectomy through Mcburney's incision under general anesthesia and by a common surgical team.

Preoperative laboratory factors were studied including complete blood count (CBC), plasma level of quantitative CRP, and fibrinogen. Plasma level of CRP was measured quantitatively by ultra-sensitive immunofluorescence technique (Biorexfars® Ltd. Co, Iran) and measurement of 10 mg/L or more considered positive. Plasma level of fibrinogen also was assayed by the Clauss technique (Merck KGaA, Germany) and reported based on mg/dL. Finally measured CRP and fibrinogen were compared among patients whose AA was pathologically confirmed.

According to previous similar study, plasma level of fibrinogen was 436 ± 40 and 391 ± 66 mg/dL in pathologically confirmed positive and negative appendicitis, respectively [13]. Regarding the latter and assumption of 50% reliability and 90% study power, then at least 32 eligible samples were needed for reliability of statistical performance. Based on positive and negative pathological report for AA, participants were simply assigned to according group for final comparison. Patients were followed until discharge from hospital and also following one week of surgery for any postoperative complication. This study was written based on the STROCCS criteria for medical articles [16].

Analysis of data was performed using the SPSS v.22. Parametric variables were introduced by mean and standard deviation. Analysis of such data was done through the independent t and also the Mann-Whithney U tests. Sensitivity and specificity of plasma factors were calculated following the ROC-curve customization and the Pearson's and the Spearman's tests examined correlation coefficient between plasma indexes and the diagnosis. Non-parametric data was stated by numbers and percent. Comparative analysis was performed through the chi squared and Fisher's exact exams. Finally the level of significant p was regarded less than 0.05.

3. Results

Finally 164 patients were enrolled. Regarding pathological study there were 96 (58.5%) and 68 (41.5%) positive and negative reports for AA, respectively. There was no obvious difference between gender, age, weight, body mass index (BMI), and race of study groups. Table 1 shows demographic findings of current study.

Laboratory data including CBC, quantitative CRP, and plasma level of fibrinogen is manifested in Table 2. Contents of the latter table imply on that plasma level of fibrinogen was significantly elevated in certainly confirmed AA.

Interestingly, despite convergence in white cell counts ($p = 0.4$) and also preference of neutrophilic cell counts ($p = 0.3$) in both groups of the study, measured either the CRP ($p = 0.03$) or plasma level of fibrinogen ($p = 0.001$) were changed concurrently. Namely, although other pathological clues except for AA could increase white cell counts with left cellular shift, increasing in whether CRP or fibrinogen occurred specifically in AA.

The ROC curve analysis and also calculated Spearman's correlation coefficient between inflammatory markers of the study and the net diagnosis of AA were presented by Table 3.

Inpatient postoperative follow up visits had no remarkable complication and all patients were discharged from the hospital with stable clinical condition.

4. Discussion

Current cohort study investigated plasma level of fibrinogen as a diagnostic criterion for AA in patients who referred to emergency department with abdominal pain and finally underwent index open appendectomy. Comparative analysis between plasma level of fibrinogen and CRP which is currently registered in diagnostic guidelines for AA showed that measured plasma level of fibrinogen could be over 66% sensitive and 93% specific when reached to 272 mg/dL or more. It's while concurrent quantitative plasma level of 21 mg/L or more for CRP was more sensitive (80%) and less specific (61%) for diagnosis of AA. Conclusively, step up approach for CRP and fibrinogen assay is highly recommended for diagnosis of AA in selected patients whose clinical and laboratory findings for AA are not correspondent. Namely, following measurement of plasma level of fibrinogen could identify presence of positive AA in patient with doubtful clinical findings except for elevated quantitative plasma level of CRP. Additionally, either increasing in white blood cell count or left cellular shift were seen in almost all differential diagnosis, elevation of plasma level of fibrinogen in concurrent to raise of CRP was occurred specifically in positive appendicitis.

Although appendectomy is performed as the most common emergent abdominal surgery following the diagnosis, incidence of missed cases are still high. Despite advancement of guidelines for diagnosis of such clinical condition, direct visual investigation through the exploratory laparoscopic approach is yet indicated in selected cases [17–19]. Measuring plasma level of fibrinogen for diagnosis of AA was focused previously. Advocates reported elevation of plasma level of fibrinogen was considerable in positive appendicitis and it reached to 436.6 ± 40.6 mg/dL [20]. They calculated the area under the ROC curve of fibrinogen around 0.697, and also 82 and 60% respective sensitivity and specificity

Table 1
Demographic data of participants based on pathological report for acute appendicitis.

Variable	Unit	Positive (n = 96)	Negative (n = 68)	P
Gender	M/F[a]	68(70.8)/28(29.2)[c]	49(72.1)/19(27.9)	0.2
Age	Year	35.4±15.2[d]	33.8 ± 15.8	0.5
Weight	kg	66.8 ± 18.3	65.9 ± 17.5	0.3
BMI	$kg.m^{-2}$	28.8 ± 11.6	28.5 ± 10.2	0.1
Race	I/NI[b]	88(91.7)/8(8.3)	63(92.6)/5(7.4)	0.1

[a] Male/female.
[b] Iranian/non-Iranian.
[c] n (%).
[d] Mean ± standard deviation.

Table 2
Laboratory data according to pathological report for acute appendicitis.

Variable	Unit	Positive (n = 96)	Negative (n = 68)	P
White cell count	Per microliter	13,320 ±3760[a]	13,740 ± 2680	0.4
Neutrophilic cell count	Per microliter	10,210 ± 1550	9980 ± 1820	0.3
C-reactive protein	mg/L	33.06 ± 16.29	21.07 ± 11.81	0.03
Fibrinogen	mg/dL	389.2 ± 229.99	142.38 ± 62.06	0.001

[a] Mean ± standard deviation.

Table 3
Data of the ROC curve analysis and Spearman's correlation coefficient.

Plasma marker	COP[b]	AUC[a]	Sensitivity	Specificity	CC[c]
C-reactive protein	21 mg/L	0.726 (p = 0.09)	80% (95% CI[d]: 75.5–86.2)	60.9% (95% CI: 51.7–68.4)	0.561 (p = 0.004)
fibrinogen	272 mg/dL	0.892 (p < 0.001)	66.7% (95% CI: 58.2–73.3)	92.8% (95% CI: 89.5–96.1)	0.698 (p = 0.04)

[a] Area under the curve.
[b] Cut-off point.
[c] Correlation coefficient.
[d] Confident interval.

for cut-off point 397 mg/dL [20]. Other study presented that serum fibrinogen could be predictable for diagnosis of complicated AA. They stated that fibrinogen value of 885 mg/dL could be the best cut-off for predicting complicated appendicitis with sensitivity of 87%, specificity of 91%, positive predictive value of 94% and, negative predictive value of 83% [21]. In lined with us, another study manifested similar results which identified a cut-off point of 245.5 mg/dL for accurate diagnosis of AA [15]. Although, some authors found no benefit for measuring serum fibrinogen and diagnosis of AA diagnosis they recommended more investigation for more appropriate judge [8].

Further for AA, plasma level of fibrinogen was also increased in upper gastrointestinal related malignancies including of gastric and esophageal carcinoma. The marker was associated with poor prognosis in malignant condition [22–23].

Considering current study and aforementioned above data, it seems that fibrinogen is relatively specific plasma marker that plays its role at prolonged highly inflammatory pathological status which its elevation is followed by occurrence of impending complication and poor prognosis. Hence, measuring serum fibrinogen in diagnosis of AA is recommended in patient following unremarkable clinical finding but with high level of quantitative CRP. In such condition, elevated plasma level of fibrinogen could be diagnostic with high specificity.

5. Limitations

This study was conducted in a section of time. All data was extracted from a unique referral health center. Although sample size was near three-fold more than calculated minimum of the need, study with larger sample size is recommended. We had no significant difference between enrolled participants' race, although the latter might influence on data. Unfortunately, available studies in literature were relatively old and issue of this paper was not comprehensively investigated recently.

6. Conclusions

Following measurement of elevated plasma level of fibrinogen could imply on presence of AA when the diagnosis of the latter is in doubt. It could be considered the next step to evaluate serum fibrinogen while the comprehension of clinical findings for the diagnosis of AA is uncertain. Measuring plasma fibrinogen for diagnosis of AA is sufficiently specific when concurrent increasing in quantitative CRP is identified but other diagnostic criteria are impotent.

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This study was conducted under order and supervision of Kashan University of Medical Sciences and all advantages referred back to this university.

Ethical approval

This study was conducted under ethics committee approval of the Kashan University of medical Sciences with the registered code IR.KAUMS.MEDNT.REC.1399.212.

Consent

Written informed consent was obtained from all participants.

Registration of research studies

This study was conducted under supervision of the Kashan University of Medical Sciences with registration code IRCT20191025616N3 which is available at www.irct.ir.

Guarantor

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Provenance and peer review

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CRediT authorship contribution statement

Shima Shafagh: Study design, Supervision, interpret results. **Mohammad Barooni:** Study design, Data collection, interpret results. **Abdulhossein Davoodabadi:** Study design, Supervision, interpret results. **Hamidreza Gilasi:** Statistical data analyzer. **Abbas Hajian:** Study design, interpret results, article draft.

Declaration of competing interest

Authors did not have any conflicts of interest in writing this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103393.

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