High Expression of C-reactive Protein Increases the Risk of Poor Prognosis in Patients with Gastric Cancer: A Meta-analysis

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Abstract: There are many researches on the correlation between C-reactive protein (CRP) and prognosis of gastric cancer, but whether CRP could be used as an evaluation indicator for prognosis of gastric cancer patients, which was still controversial. Therefore, we conducted meta-analysis based on 18 studies involving 3656 objects. The results show that, CRP was significantly correlated with the risk of poor prognosis of gastric cancer patients \[HR (95\%CI) 1.50 (1.24, 1.81) P=0.000\] , and the risk of the poor prognosis can be significantly increased when CRP>10mg/L. In the different clinical stage, high expression of CRP can increases the risk of poor prognosis. The CRP can be used as an important indicator of poor prognosis of gastric cancer patients.

Keywords: C-reactive Protein, Gastric Cancer, Prognosis, Meta-analysis

1. Introduction

Gastric cancer is one of the most common malignant tumors in humans, which ranks the fourth highest malignant tumor in the world, and the associated mortality rate takes the second place [1]. Mortality and mortality of gastric cancer are the highest and increasing year by year in China [2]. The treatment of gastric cancer currently includes surgical resection, chemotherapy, radiotherapy, and other comprehensive treatment measures, but the prognosis is still poor, and the overall 5-year survival rate usually does not exceed 20% [3].

In tumor tissue, cells are present in the microenvironment similar to chronic inflammation. Persistent inflammatory reactions occur in the microenvironment, which produces inflammatory media and continues to aggravate the inflammatory state of the tumor microenvironment. Moreover, cancer infiltration induces local tissue destruction, interferes with tissue homeostasis, and leads to systemic inflammatory reactions. Systemic inflammatory reaction has positive feedback with cancer invasion and metastasis. Abdominal metastasis of gastric cancer leads to abdominal cavity adhesion and obstruction of blood vessels, intestine and bile ducts, which aggravates systemic inflammation reactions [4].

C-reactive protein (CRP) is an acute phase protein
synthesized by hepatocytes, which increases in inflammatory diseases. Later studies show that the elevated levels of CRP are associated with an increased risk of colon cancer, lung cancer, prostate cancer and ovarian cancer [5]. Baba et al [6] found that CRP is a risk factor for poor prognosis of gastric cancer stage IV. However, some studies do not support this association. Aizawa et al [7] believed the CRP is not an independent risk factor for prognosis of gastric cancer patients in stage I-III (\(P=0.072\)). Fujitani et al [8] found there is no correlation between CRP and poor prognosis of gastric cancer patients (\(P=0.497\)). Therefore, in here we evaluates the relationship between CRP and risk of poor prognosis of gastric cancer patients by a comprehensive meta-analysis, so as to search for an important indicator of poor prognosis of gastric cancer patients.

2. Methods

2.1. Search Strategy

The literature search process is shown in Figure 1. Two investigators (Qian-Long Zhao and Jun-Yi Chen) independently searched the literature using PubMed, Embase, The Cochrane Library, Chinese Biomedical Literature Database (CBM), China Knowledge Resource Integrated Database (CNKI), VIP Database, and WanFang Database, from their inception to February 10th 2018. Search terms included “C-reactive protein” “C reactive protein” “CRP” “stomach neoplasms” “gastrectomy” “gastrointestinal cancer” “gastrointestinal malignancies”. These literature included full articles, review articles and meta-analyses in this area, which were searched for citations of further relevant published and unpublished research.

![Flow diagram of the studies included and excluded in the Meta-analysis.](image)

2.2. Inclusion and Exclusion Criteria

Literature met the following requirements were included: 1) patients were diagnosed clinically with gastric cancer; 2) the study was designed as a cohort study; 3) the report of the study should provide correlation between the CRP levels and the hazard ratio (HR) or the relative risk (RR) of the prognosis of gastric cancer patients. Or the raw data provided can be used to calculate the HR. In addition, Repeated report should be excluded. The latest report would be included if the same cohort study repeated many times at different time points.

Exclusion criteria were as follows: 1) animal studies; 2) literature review summary; 3) the follow-up time is less than 1 month; 4) literature were not provided data on survival prognosis; 5) research and design have defects with incomplete data.

| Study                | Year | Sample size | Gender (M/F) | Age       | Follow-up (months) |
|----------------------|------|-------------|--------------|-----------|-------------------|
| Albanopoulos et al   | 2013 | 177         | 75/102       | 38.1 (18-61) | 1                 |
| Baba et al           | 2013 | 123         | 91/32        | 69 (26-88)  | 60                |
| Chang et al          | 2010 | 170         | 112/58       | 65.1 (29-89) | 68.5              |
| Jeong et al          | 2012 | 104         | 69/35        | 52.5 (28-82) | 11.9              |
| Mohri et al          | 2010 | 357         | 245/112      | 63.4 (32-87) | 68                |
| Aizawa et al         | 2011 | 262         | 180/82       | 64         | 54.5              |
| Nozoe et al          | 2011 | 204         | 142/62       | 67 (27-89)  | 60                |
Table 1. Continued.

| Study          | TNM | Treatment method | Country   | Cut-off level (CRP) | Quality assessment |
|----------------|-----|------------------|-----------|---------------------|-------------------|
| Albanopoulos et al | IV  | Reduction surgery | Greece    | 5                   | 7                 |
| Baba et al      | IV  | Reduction surgery | Japan     | 17                  | 7                 |
| Chang et al     | I-IV| Multiple therapies | China     | 3                   | 7                 |
| Jeong et al     | IV  | NS                | Korea     | 10                  | 6                 |
| Mohri et al     | I-III| Radical surgery   | Japan     | 3                   | 7                 |
| Aizawa et al    | I-III| Radical surgery   | Japan     | 10                  | 7                 |
| Nozoe et al     | I-III| Radical surgery   | Japan     | 5                   | 7                 |
| Hashimoto et al | I-IV| Reduction surgery | Japan     | 10                  | 7                 |
| Ishino et al    | I-III| Reduction surgery | Japan     | 5                   | 7                 |
| Fujitani et al  | I-IV | Multiple therapies | Japan     | 3                   | 7                 |
| Saito et al     | IV  | surgery           | Japan     | 120                 | 7                 |
| Shimure et al   | IV  | Chemical therapy  | Japan     | 10                  | 7                 |
| Iwasa et al     | IV  | NS                | Japan     | 20                  | 6                 |
| Wang et al      | III | Radical surgery   | China     | 10                  | 8                 |
| Hwang et al     | IV  | NS                | Korea     | 10                  | 8                 |
| Kwon et al      | I-IV | Multiple therapies | Korea     | 10                  | 7                 |
| Zhang et al     | III-IV| Chemical therapy | China     | 10                  | 7                 |
| Zhu et al       | III-IV| Radical surgery   | China     | 10                  | 7                 |

+ NA: Not available; NOS: The quality score by Newcastle-Ottawa Scale; RS: Reduction surgery; Mt: Multiple therapies; NS: Non-surgery; Ct: Chemical therapy.

2.3. Data Extraction

After removing the duplicates, two investigators (Fu-Lun Li and Ke Liu) independently screened the title and abstracts of all records, and then selected the articles that fulfilled the inclusion criteria. Any uncertainties were resolved by consensus or with a third reviewer (Jing Yang).

A predefined excel table was used to extract information about relevant characteristics of included studies such as title, the first author, publication year, sample size, age/gender of participants, follow-up times, TNM stage, treatment method, and quality assessment.

2.4. Quality Assessment

The quality of the methodology of the included studies was assessed by the Newcastle-Ottawa scale (NOS) recommended by the Cochrane Non-Randomized Studies Methods Working Group. Studies with scores of ≥6 were defined as high quality studies. Quality assessment was performed by two investigators (Fu-Lun Li and Ke Liu) independently. Disagreements were resolved by discussion.

2.5. Statistical Analysis

The pooled HR and its 95% confidence interval (95%CI) was used to evaluate the correlation between CRP and poor prognosis of gastric cancer patients; subgroup analysis was also performed by sample size, follow-up times, TNM stage and treatment method. Heterogeneity between studies was detected by the Q test and the I² metric (no heterogeneity: I²=0%-25%; moderate heterogeneity: 25%-50%; large heterogeneity: 50%-75%; and extreme heterogeneity: 75%-100%). A fixed effect model analysis was performed when P≥0.10 in the Q test or when I²<50%, otherwise a random effect model analysis was conducted. Publication bias were tested by the Begg's funnel plot. All P values were two-tailed and a P value less than 0.05 were considered statistically significant. Most of the statistical analyses in this study were conducted by the STATA software (version 11.2; Stata Corp, College Station, Texas USA).

3. Results

3.1. Search Results and Characteristics of Studies

Of 226 eligible papers identified in literature search, 18 papers [4, 6-22] fulfilled the inclusion criteria after screening the titles, abstracts and full texts, and removing the duplicates (shown in Figure 1). 16 of these studies were published in English and 2 in Chinese. Their sample size ranged from 53 to 466 subjects. The 18 included studies had a total 3656 subjects of which 2330 (63.70%) were males. Follow-up...
times ranged from 1 month to 10 years. Moreover, all studies that scored $\geq 6$ were considered to be of higher quality, which could be used for a meta-analysis (shown in Table 1).

3.2. CRP and the Poor Prognosis of Gastric Cancer Patients

18 studies evaluating the correlation between CRP level and the poor prognosis of gastric cancer patients existed statistical heterogeneity ($I^2 = 85.2\%$, $P<0.001$). Therefore, the random effects model was used for meta-analysis. The results show that, CRP was significantly correlated with the poor prognosis of gastric cancer patients, high expression of C-reactive protein increases the risk of poor prognosis in patients with gastric cancer ($HR (95\% CI) = 1.50 (1.24, 1.81)$)

3.3. Subgroup Analyses of the Poor Prognosis of Gastric Cancer Patients

Subgroup analyses on sample size. As depicted in Table 2, the sample size was $\geq 200$, and there was statistical heterogeneity among the results of studies, so random effect model was used for analysis, $HR (95\% CI) = 1.78 (1.13, 2.81)$. Whereas, the sample size was $<200$, the random effect model is also adopted, $HR (95\% CI) = 1.34 (1.10, 1.63)$. There is no statistical difference between the sample size ($P>0.05$). It suggested that the sample size included in the study will not affect the risk of the poor prognosis of gastric cancer patients.

Subgroup analyses on treatment method. As depicted in Table 2, the follow-up times of year $\geq 5$ and $<5$ were considered to be of higher quality, which was significant heterogeneity. Using a random effects model, the follow-up times of year $\geq 5$ and $<5$ were $2.81 (1.46, 5.13)$ and $1.12 (0.73, 1.71)$ respectively. Therefore, it suggested the follow-up times will not affect the risk of the poor prognosis of gastric cancer patients.

Subgroup analyses on follow-up times. As depicted in Table 2, the follow-up times (years $\geq 5$ or $<5$) was significant heterogeneity. Using a random effects model, the follow-up times of year $\geq 5$ and $<5$ were $2.81 (1.46, 5.13)$ and $1.12 (0.73, 1.71)$ respectively. Therefore, it suggested the follow-up times will not affect the risk of the poor prognosis of gastric cancer patients.

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Table 2, the significant differences were seen in the radical surgery group as calculated by the random effect model, HR (95%CI) was 1.40 (1.08, 1.80). Whereas, the non-operative treatment adopted the fixed effect model, HR (95%CI) was 1.68 (1.44, 1.97). There is no statistical difference between the treatment (P=0.05). It suggested the treatment method will not affect the risk of poor prognosis of gastric cancer patients.

Subgroup analyses on TNM stage. Using a random effects model, HR (95%CI) was 1.47 (1.15, 1.86) in the stage IV. Whereas, the stage I-III adopted the fixed effect model, HR (95%CI) was 2.23 (1.76, 2.82). There is no statistical difference between the TNM stage (P>0.05). It suggested the TNM stage will not affect the risk of poor prognosis of gastric cancer patients (shown in Table 2). In addition, it is observed that the HR (95%CI) is 1.47 (1.15, 1.86) and 2.23 (1.76, 2.82) in the stage IV and I-III, so in the different stage, high expression of C-reactive protein can increases the risk of poor prognosis in patients with gastric cancer.

Table 2. Subgroup analyses for C-reactive protein and the risk of poor prognosis of gastric cancer patients.

| Subgroup          | Number of cohorts | HR (95%CI), P  | P value | I²% |
|-------------------|-------------------|----------------|---------|-----|
| Sample size       |                   |                |         |     |
| ≥200              | 8                 | 1.78 (1.13, 2.81), 0.013 | 0.879 | 89.8 |
| <200              | 10                | 1.34 (1.10, 1.63), 0.004 | 78.3   |
| Follow-ups (years)|                   |                |         |     |
| ≥5                | 6                 | 1.61 (1.15, 2.26), 0.006 | 78.4   |
| <5                | 12                | 1.49 (1.11, 2.00), 0.008 | 88.0   |
| Treatment         |                   |                |         |     |
| Radical surgery   | 10                | 1.40 (1.08, 1.80), 0.010 | 87.6   |
| Non-surgery       | 3                 | 1.68 (1.44, 1.97), 0.000 | 0.0    |
| TNM stage         |                   |                |         |     |
| IV                | 7                 | 1.47 (1.15, 1.86), 0.002 | 87.7   |
| I-III             | 5                 | 2.23 (1.76, 2.82), 0.000 | 0.0    |

3.4. Multi-Factorial Analysis of the Poor Prognosis of Gastric Cancer Patients

Multiple factors affecting the risk of poor prognosis of gastric cancer patients included gender, age (years), lymphatic invasion, peritoneal metastasis and recurrence. As depicted in Table 3, it suggested that gender, age (years), lymphatic invasion were not the influencing factors of the poor prognosis of gastric cancer patients (P>0.05), HR (95%CI) for gender, age (years) and lymphatic invasion were 1.04 (0.93, 1.17), 1.00 (0.87, 1.14) and 1.18 (0.64, 2.16) respectively. Whereas, HR (95%CI) for peritoneal metastasis and recurrence were 2.85 (1.26, 6.46) and 3.61 (2.46, 5.28), It showed peritoneal metastasis and recurrence are risk factors of the poor prognosis of gastric cancer patients (P<0.05) (shown in Figure 3).

Table 3. Multivariate analysis for the risk of poor prognosis of gastric cancer patients.

| Factors          | Analysis | Number of cohorts | HR (95%CI), P  | P value | I²% |
|------------------|----------|-------------------|----------------|---------|-----|
| Gender           | Male VS Female | 11              | 1.04 (0.93, 1.17), 0.367 | 27.4   |
| Age (years)      | <60 VS ≥60 | 5                | 1.00 (0.87, 1.14), 0.949 | 0.0    |
| Lymphatic invasion | Yes VS No | 4                | 1.18 (0.64, 2.16), 0.990 | 59.6   |
| Peritoneal metastasis | Yes VS No | 3                | 2.85 (1.26, 6.46), 0.012 | 88.7   |
| Recurrence       | Yes VS No | 2                | 3.61 (2.16, 5.28), 0.000 | 0.0    |

Figure 3. Peritoneal metastasis and recurrence for the risk of the poor prognosis of gastric cancer patients.
3.5. Sensitivity Analysis of the Meta-analysis

As depicted in Figure 4. Sensitivity analysis indicated that the results of the meta-analysis were stable.

3.6. Publication Bias Analysis of the Meta-analysis

The potential reasons of Begg’s test to detect the publication bias. Each divergence point was basically symmetrically dispersed, and it was an inverted funnel shape \( (P=0.131) \), suggesting that the possibility of publication bias was less (shown in Figure 5).

4. Discussion

Cancer-associated inflammation is modulated by cancer cells themselves, host stromal cells, and their interactions. The CRP was an acute phase protein synthesized by hepatocytes, which reflected a measure of the acute phase response [23]. The molecular mechanism of the correlation between CRP and prognosis of cancer is complex and has not yet been fully clarified. The mechanism was more widely recognized that cancer can raise CRP levels, and CRP promotes the occurrence and development of cancer. The mechanism of elevation of CRP caused by cancer was: Inflammatory mediators and cytokines were produced or released by endogenous and exogenous stimuli, such as cancer. Activated inflammatory cells released TNF and IL-1, which acted on lymphocytes and stromal cells to release IL-
6, IL-8 and macrophage inflammatory proteins. These cytokines acted on blood vessels, including the liver, to produce acute phase reaction proteins such as CRP [24, 25]. The mechanism of promoting cancer development by CRP was: Chronic inflammation and oxidative stress inactivated cancer suppressor genes or inhibited protein post-translational modifications (PTMs) regulating DNA repair and apoptosis; inflammatory cytokine signals promoted the proliferation of cancer cells and inhibited apoptosis of cancer cells via intracellular enzymes and transcription factors. Moreover, activation of inflammatory pathways can promote cell migration, vascular infiltration and angiogenesis, further accelerate cancer progression [26, 27].

An effective prognostic indicator could not only predict the survival condition, but also provide guidance for doctors in the selection of clinical treatment, correct selection of clinical treatment method would improve the quality of life in patients. At present, there are many researches on the correlation between CRP level and gastric cancer, but whether CRP could be used as an evaluation indicator for prognosis of gastric cancer patients, which was still controversial. Therefore, we deeply analyzed the published cohort study on CRP lever and the risk of poor prognosis of gastric cancer patients, in order to determine the dose-relationship between CRP and the risk of poor prognosis of gastric cancer patients.

There had been a lot of researches on the correlation between CRP and the occurrence or prognosis of gastric cancer at home and abroad. Baba et al. [8] found CRP was a risk factor for poor prognosis of gastric cancers in stage IV \( \text{HR} \ (95\% \text{CI}) \ 1.11 \ (1.03, \ 1.18) \), which was consistent with our study results \( \{\text{HR} \ (95\% \text{CI})=1.50, \ (1.24, \ 1.81)\} \). Baba et al. [8] found the optimal critical value of CRP was 17mg/L by ROC curve. That is to say when CRP>17mg/L, the risk of the poor prognosis of gastric cancer patients was significantly increased. Meanwhile our study also found that when the critical value of CRP was 10mg/L and 17mg/L, the risk of poor prognosis was lower than others. A recent Meta study [28] found that when CRP>10mg/L, accompany with the increase of CRP the risk of the poor prognosis of gastric cancer patients was significantly increased, which was consistent with our study results. Subgroup analysis showed that in the different stage, high expression of C-reactive protein can increases the risk of poor prognosis of gastric cancer patients. Multivariate analysis showed that peritoneal metastasis and recurrence could increase the risk of poor prognosis of gastric cancer patients, which is consistent with that obtained by Yu [28].

5. Conclusions

In conclusion, this study showed that: 1) the CRP lever was closely related to the risk of poor prognosis of gastric cancer patients; 2) when CRP>10mg/L, CRP can be used as an important indicator of poor prognosis of gastric cancer patients; 3) in the different clinical stage high expression of C-reactive protein both can increase the risk of poor prognosis of gastric cancer patients; 4) multivariate analysis showed that peritoneal metastasis and recurrence were the factor independently associated with prognosis of gastric cancer patients.

In the future, more high-quality, multi-center and large-scale clinical trials need to be carried out to further prove this result. It is believed that breakthrough progress will be made in evaluating the prognosis of gastric cancer patients, and early intervention treatment will improve the quality of life of cancer patients.

Conflicts of Interest

1) All the authors do not have any possible conflicts of interest.
2) The authors declare that they have no competing interests.

References

[1] Parkin DM, Pisani P, et al. Global cancer statistics. CA; a cancer journal for clinicians. 2005; 55; 74-108.
[2] Yang HP, Zhang CQ. Research progress in gene therapy of gastric cancer. Journal of Modern Oncology. 2008; 16 (6); 1058-61.
[3] Rossomando AJ, Sanghera JS, et al. Biochemical characterization of a family of serine/threonine protein kinases regulated by tyrosine and serine/threonine phosphorylations. Journal of Biological Chemistry. 1991; 266 (30); 20270-5.
[4] Zhang Yj, Zhu ZY, et al. Study on relationship of C-reactive protein with peritoneal cavity metastasis and prognosis of gastric carcinoma. Chinese Clinical Oncology. 2015; 20 (6); 535-9.
[5] Roxburgh CS, Mcmillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncology. 2010; 6 (1); 149-63.
[6] Baba H, Kuwabara K, et al. C-reactive protein as a significant prognostic factor for stage IV gastric cancer patients. Anticancer Research. 2013; 33 (12); 5591-5.
[7] Aizawa M, Gotohda N, et al. Predictive Value of Baseline Neutrophil/Lymphocyte Ratio for T4 Disease in Wall-Penetrating Gastric Cancer. World Journal of Surgery. 2011; 35 (12); 2717-22.
[8] Fujitani K, Yamada M, et al. Optimal indications of surgical palliation for incurable advanced gastric cancer presenting with malignant gastrointestinal obstruction. Gastric Cancer Official Journal of the International Gastric Cancer Association & the Japanese Gastric Cancer Association. 2011; 14 (4); 353-9.
[9] Albanopoulos K, Alevizos L, et al. C-reactive protein, white blood cells, and neutrophils as early predictors of postoperative complications in patients undergoing laparoscopic sleeve gastrectomy. Surgical Endoscopy. 2012; 27 (3); 864-71.
[10] Chang CC, Sun CF, et al. Preoperative serum C-reactive protein and gastric cancer; Clinical-pathological correlation and prognostic significance. Chang Gung Medical Journal. 2010; 33 (3); 301-12.
[11] Hashimoto K, Takashima A, et al. Prognosis-free survival in first-line chemotherapy is a prognostic factor in second-line chemotherapy in patients with advanced gastric cancer. Journal of Cancer Research & Clinical Oncology. 2010; 136 (7); 1059-64.

[12] Hwang JE, Kim HN, et al. Prognostic significance of a systemic inflammatory response in patients receiving first-line palliative chemotherapy for recurrent or metastatic gastric cancer. Bmc Cancer. 2011; 11 (1); 1-7.

[13] Ishino Y, Saigusa S, et al. Preoperative C-reactive protein and operative blood loss predict poor prognosis in patients with gastric cancer after laparoscopy-assisted gastrectomy. Asian Journal of Endoscopic Surgery. 2014; 7 (4); 287-94.

[14] Iwasa S, Nakajima TE, et al. Systemic chemotherapy for peritoneal disseminated gastric cancer with inadequate oral intake; a retrospective study. International Journal of Clinical Oncology. 2011; 16 (1); 57-62.

[15] Jeong J, Lim SM, et al. Comparison of two inflammation-based prognostic scores in patients with unresectable advanced gastric cancer. Oncology. 2012; 83 (5); 292-9.

[16] Kwon HC, Kim SH, et al. Clinicopathologic significance of expression of nuclear factor-kB RelA and its target gene products in gastric cancer patients. World Journal of Gastroenterology. 2012; 18 (34); 4744-50.

[17] Mohri Y, Miki C. Reply; Prognostic Significance of Host- and Tumor-related Factors in Patients with Gastric Cancer. World Journal of Surgery. 2010; 34 (2); 285-90.

[18] Nozoe T, Iguchi T, et al. Preoperative elevation of serum C-reactive protein as an independent prognostic indicator for gastric cancer. Surgery Today. 2011; 41 (4); 510-3.

[19] Takuro Saito MD, FACS YKM, et al. Which is a more reliable indicator of survival after gastric cancer surgery; Postoperative complication occurrence or C-reactive protein elevation? Journal of Surgical Oncology. 2015; 112 (8); 894-9.

[20] Shimura T, Kitagawa M, et al. C-reactive protein is a potential prognostic factor for metastatic gastric cancer. Anticancer Research. 2012; 32 (2); 491-496.

[21] Wang DS, Ren C, et al. Comparison of the prognostic value of various preoperative inflammation-based factors in patients with stage III gastric cancer. Tumor Biology. 2012; 8 (33); 749-56.

[22] Zhu M, Wei J, et al. Correlation between serum C-reactive protein level and prognosis of advanced gastric cancer. Guizhou Medical Journal. 2016; 40 (3); 249-50.

[23] Yamashita H, Katai H. Systemic Inflammatory Response in Gastric Cancer. World Journal of Surgery. 2010; 34 (10); 2399-400.

[24] Groblewska M, Mroczko B, et al. Interleukin 6 and C-reactive protein in esophageal cancer. Clinica Chimica Acta. 2012; 413 (19-20); 1583-90.

[25] Kwon KA, Kim SH, et al. Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer. Bmc Cancer. 2010; 10 (10); 203-06.

[26] Rieland M, Cantor DJ, et al. Senescence-associated SIN3B promotes inflammation and pancreatic cancer progression. Journal of Clinical Investigation. 2014; 124 (5); 2125-35.

[27] Hasselbalch HC. Perspectives on chronic inflammation in essential thrombocythemia, polycythemia vera, and myelofibrosis; is chronic inflammation a trigger and driver of clonal evolution and development of accelerated atherosclerosis and second cancer? Blood. 2012; 119 (14); 3219-25.

[28] Yu Q, Yu XF, et al. Prognostic role of C-reactive protein in gastric cancer; a meta-analysis. Asian Pacific Journal of Cancer Prevention Apjcp. 2013; 14 (10); 5735-40.