University of Saad Dahlab

Graduation Project

Diagnosis of Disseminated Intravascular Coagulation

Authors:
Benzid Chaima
Ahmine Kahina
Azzouzi Khadoudj

Supervisor:
H. Hamel

President: F. Ghellai
Examiner: M. Mihoub

Doctor of Pharmacy

in the

November 18, 2020

Declaration of Authorship

We, Benzid Chaima, Ahmine Kahina, Azzouzi KHADOUDJ, declare that this thesis titled, "Diagnosis of Disseminated Intravascular Coagulation" and the work presented in it are our own. We confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where any part of this project has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
- Where we have consulted the published work of others, this is always clearly attributed.
- Where We have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely our own work.
- We have acknowledged all main sources of help.

Signed:

Date:

"*As we let our own light shine, we unconsciously give other people permission to do the same.*"

Nelson Mandela

Abstract

Disseminated Intravascular Coagulation (DIC) is an acquired syndrome characterized by intravascular coagulation activation with a loss of localization, which can lead to severe bleeding or thrombotic problems and it is due to different causes. The cornerstone of management remains the early and effective etiological treatment. DIC is known to complicate many cancers, especially hematological ones. Its clinical manifestations can go from asymptomatic to fulminant, and it is often associated with poor prognosis. Our work consists of a literature review. We collected data from several data base. This work aims to gather information about the occurrence of DIC in cancer patients, and to compare between different diagnostic criteria used mainly in solid cancer patients as well as patients with hematological malignancies. The occurrence of DIC depends on the cancer type, stage, complication by metastasis and the histological characteristics of tumor, age and gender. High incidence was observed in APL and metastatic prostate cancer. Studies have found that global coagulation tests, specific tests or the scoring system are not sufficiently reliable to diagnose DIC, either because of their availability, sensitivity and specificity, or their usefulness in an emergency situation. Although new tests are still being evaluated (TEG, ROTEM, APTT biphasic wave...), it is still difficult today to find a gold standard that can diagnose DIC with any underlying disease, at an early stage, and that can be easy to use in emergency situations.

La Coagulation Intravasculaire Disséminée (CIVD) est un syndrome acquis caractérisé par une activation de la coagulation intravasculaire avec perte de localisation, qui peut entraîner de graves saignements ou des problèmes thrombotiques et qui est due à différentes causes. La pierre angulaire de la prise en charge reste le traitement étiologique précoce et efficace. La CIVD est connue pour compliquer de nombreux cancers, notamment hématologiques. Ses manifestations cliniques peuvent aller d'asymptomatiques à fulminantes, et elle est souvent associée à un mauvais pronostic. Notre travail consiste à faire une analyse de la littérature que nous avons recueillie à partir de plusieurs bases de données. Ce travail vise à rassembler des informations sur l'apparition de la CIVD chez les patients cancéreux, et à comparer les différents critères de diagnostics utilisés principalement chez les patients atteints de cancer solides ainsi que chez les patients atteints de malignités hématologiques. L'incidence de la CIVD dépend du type de cancer, du stade, de la complication par métastases et des caractéristiques histologiques de la tumeur, de l'âge et du sexe. Une incidence élevée a été observée dans le cas du cancer de la prostate métastatique et de l'LPA. Nous avons constaté, sur la base des résultats précédents, que les tests de coagulation globaux, les tests spécifiques ou le système de notation ne sont pas suffisamment fiables pour diagnostiquer une CIVD, soit en raison de leur disponibilité, de leur sensibilité et de leur spécificité, soit en raison de leur utilité dans une situation d'urgence. Bien que de nouveaux tests soient encore en cours d'évaluation (TEG, ROTEM, APTT onde biphasique...), il est encore difficile aujourd'hui de trouver une référence qui permette de diagnostiquer la CIVD avec n'importe quelle maladie sous-jacente, à un stade précoce, et qui soit facile à utiliser dans les situations d'urgence.

Acknowledgements

We want to thank our families and friends and all the people that supported us through these years. We also want to express our deep gratitude to our supervisor that supported us and encouraged us in each step that we took to finalize this humble work ...

Contents

Appendices i

Declaration of Authorship ii

Introduction iii

Abstract iv

Acknowledgements v

1 Physiological Recall 3
- 1.1 Haemostasis . . . 3
- 1.2 Phase 1: Primary Haemostasis . . . 3
  - 1.2.1 Vasoconstriction . . . 3
  - 1.2.2 Platelet Plug Formation . . . 3
  - 1.2.3 Platelet Adhesion . . . 3
  - 1.2.4 Platelet Activation . . . 3
  - 1.2.5 Platelet Aggregation . . . 4
- 1.3 Phase 2: Coagulation Physiology . . . 4
  - 1.3.1 Coagulation Pathway . . . 4
  - 1.3.2 Fibrin Clot Formation . . . 6
- 1.4 Regulation of Coagulation . . . 7
  - 1.4.1 Serpins . . . 7
  - 1.4.2 Other Inhibitors . . . 8
- 1.5 Phase 3: Fibrinolysis . . . 8
  - 1.5.1 Fibrinolysis Actors . . . 8
  - 1.5.2 Fibrinolysis Steps . . . 8

2 Exploration of Haemostasis 11
- 2.1 Primary Haemostasis . . . 11
  - 2.1.1 Platelet Enumeration . . . 11
  - 2.1.2 Bleeding Time . . . 11
  - 2.1.3 The Time of Occlusion . . . 11
  - 2.1.4 Study of Membrane Receptors by Flow Cytometry . . . 11
- 2.2 Exploration of Coagulation . . . 12
  - 2.2.1 Activated Partial Thromboplastin Time (APTT) . . . 12
  - 2.2.2 Prothrombin Time . . . 12
  - 2.2.3 Specific Dosages of Coagulation Factors . . . 12
  - 2.2.4 Fibrinogen Assay . . . 13
  - 2.2.5 Determination of coagulation inhibitors: . . . 13
- 2.3 Exploration of Fibrinolysis . . . 13
  - 2.3.1 Global Tests . . . 13
  - 2.3.2 Determination of Fibrinolysis Factors . . . 13

3 Disseminated Intravascular Coagulation **14**
3.1 Definition . . . 14
3.2 Epidemiology . . . 14
3.3 Pathophysiology . . . 15
3.3.1 Risk Factors for DIC . . . 15
3.3.2 DIC Mechanisms . . . 16
3.4 Clinical Manifestations . . . 18
3.4.1 Bleeding . . . 18
3.4.2 Thrombosis . . . 19
3.5 Complications of DIC . . . 19
3.5.1 Multiple Organ Failure Syndrome (MOFS) . . . 19
3.5.2 Systemic Inflammatory Response Syndrome (SIRS) . . . 20
3.6 DIC in Cancer . . . 21
3.6.1 Definition of Cancer . . . 21
3.6.2 Complications of Cancer . . . 21
3.6.3 Pathophysiology of DIC in Cancer . . . 22
3.7 Diagnosis of DIC . . . 23
3.7.1 Global Coagulation Tests in DIC . . . 24
3.7.2 Confirmatory Tests for the Diagnosis of DIC . . . 25
3.7.3 Other Markers of Haemostasis . . . 26
3.7.4 Other Biological Abnormalities . . . 26
3.7.5 Scoring Systems . . . 27
3.7.6 Differential Diagnosis of DIC, Coagulation Defect due to Liver Failure and Primary Pathological Fibrinolysis . . . 31
3.8 Treatment of DIC . . . 31
3.8.1 Replacement of Blood Products . . . 32
3.8.2 Anticoagulants . . . 33
3.8.3 Coagulation Inhibitors . . . 34
3.8.4 Fibrinolytic Inhibitors . . . 34
3.8.5 Recombinant Activated Factor VII (Novoseven®) . . . 37
3.9 Management of DIC in Cancer Patients . . . 37

4 Material and Methods **39**
4.1 Material and Methods 1: Review of the literature . . . 39
4.2 Material and Methods 2: Practical Section . . . 41
4.2.1 Material . . . 41
4.2.2 Methods . . . 41

5 Results **44**
5.1 Group 1: Solid Cancer . . . 45
5.1.1 Patients' Characteristics . . . 45
5.1.2 Tumor Sites Studied in the Solid Cancer Population: . . . 46
5.1.3 Diagnostic Criteria for DIC . . . 47
5.1.4 Laboratory Findings in DIC Patients . . . 48
5.1.5 Laboratory Findings in Patients without DIC . . . 50
5.1.6 DIC frequency: . . . 52
5.1.7 Complications . . . 53
5.1.8 Comparison of Laboratory Findings between DIC + and DIC – Groups: . . . 54
5.2 Group 2: Hematological Malignancies . . . 57
5.2.1 Patients' Characteristics . . . 57

5.2.2 Distribution of Population According to Cancer Type 58
5.2.3 Diagnostic Criteria 59
5.2.4 Laboratory Findings in DIC Patients 60
5.2.5 Laboratory Findings in non-DIC Patients 62
5.2.6 DIC Frequency 64
5.2.7 Complications 64
5.2.8 Comparison between DIC and non-DIC patients 65
5.2.9 Comparison between Risk Factors in DIC+ and DIC- Groups . 67
5.2.10 Comparison between Complications in DIC+ and DIC- Groups 67
5.3 The Relevance of using Scores in the Diagnosis of DIC 68
5.3.1 Comparison between Global Coagulation Tests and Scores . . . 69
5.3.2 Comparison between Scoring Systems 75
5.4 Cancer and pre-DIC 79
5.5 Scores and Non-overt DIC 80
5.6 Practical Section 86
5.6.1 Patients' Characteristics 86
5.6.2 Cancer Type 86
5.6.3 Laboratory Findings 86
5.6.4 Hematimetric Parameters 86
5.6.5 Hemostatic Parameters 87
5.6.6 Distribution of Patients according to Abnormal Biological Parameters: 87
5.6.7 Relation between Score Values and Biological Parameters . . . 89
Correlation between Laboratory Findings in Control 2 and Score 3 Values 89
5.6.8 Relation between Complications and the Presence or Absence of Non-overt DIC 90
5.6.9 Relation between Risk Factors and the Presence or Absence of Non-overt DIC 90

6 Discussion **91**

7 Conclusion **94**

A Appendices **95**
A.1 Appendice A 95
A.2 Appendix B 96
A.3 Appendix C 97

Bibliography **99**

List of Figures

1.1 Haemostasis Pathway learning objectives 2020 . . . 4
1.2 Another way of Activation of Factor XI via Contact Protein (Robert S. Hillman, Kenneth A. Ault, Michel Leporrier 2011) . . . 6
1.3 Fibrinogen Structure (Vaez-ghaemi et al. 2017) . . . 7
1.4 Fibrignogen Degradation by Plasmin Harif 2015 . . . 9
1.5 Fibrinogen Degradation Nougier and Marijon 2012 . . . 9
1.6 Fibrinolysis by Formation of Plasmin, Inhibitors and Activators of Fibrinolysis Process (*Fibrinolysis*) . . . 10

2.1 In vitro coagulation testing. Activated partial thromboplastin time (APTT) explores endogenous and common pathway factors; prothrombin time (PT) explores tissue factor VII and common pathway factors (Revel and Doghmi 2004) . . . 12

3.1 The Abnormal Haemostatic Systems in DIC . . . 17
3.2 Classification of Disseminated Intravascular Coagulation Types . . . 18
3.3 Four Types of DIC . . . 18
3.4 Clinical Manifestation of DIC *CM1* . . . 19
3.5 Clinical Manifestation of DIC *CM2* . . . 19
3.6 Evolution of SIRS to MODS (Du Pont-Thibodeau et al. 2014) . . . 20
3.7 Schematic Representation of Pathogenetic Pathways in Disseminated Intravascular Coagulation during Systemic Inflammatory Response syndromes . . . 20
3.8 Five-step Algorithm for the Diagnosis of Disseminated Intravascular Coagulation (Lippi 2006) . . . 24
3.9 Scoring System for Non-overt Disseminated Intravascular Coagulation (Takemitsu et al. 2010) . . . 30
3.10 Flowchart for the Diagnostic and Therapeutic Management of DIC Facts 2020 . . . 32

A.1 Technical Data Form (page1) . . . 97
A.2 Technical Data Form (page2) . . . 98

List of Tables

1.1 Coagulation Factors Harif 2015 5

3.1 Clinical Conditions most Frequently Associated with DIC Facts 2020 . 15
3.2 Initial Laboratory Tests in the Diagnosis of DIC Karpatkin 1971 . . . 23
3.3 Laboratory Values for DIC 26
3.4 The Diagnostic Criteria for DIC by the Japanese Ministry of Health and Welfare (JMHW) Sugawara et al. 2013 28
3.5 Japanese Association for Acute Medicine Scoring System (Takemitsu et al. 2010) 29
3.6 Scoring System for Overt Disseminated Intravascular Coagulation (Hayakawa et al. 2007) 30
3.7 Laboratory Differential Diagnosis between Disseminated Intravascular Coagulation (DIC), Liver Disease not Accompanied by DIC, and Primary Fibrinolysis Karpatkin 1971 31
3.8 Clinical Trials for DIC or Severe Sepsis Wada 2004 33
3.9 Studies on Anticoagulant Factor Concentrates Gando et al. 2016 . . . 36
3.10 Final Recommendation for the Treatment of DIC Squizzato and Wada 2015 37
3.11 Approaches for Management of Patients with Disseminated Intravascular Coagulation and Hematologic Franchini et al. 2010 38

5.1 Epidemiologic Data of Solid Cancer Population in Selected Studies . . 45
5.2 Distribution of Solid Cancer Population According to Tumor Sites . . 46
5.3 DIC Diagnostic Criteria in Selected Studies 47
5.4 Global Coagulation Tests Results in Solid Cancer Patients with DIC . 48
5.5 Hemostatic Markers in Patients with DIC 49
5.6 Global Coagulation Tests in Solid Cancer Patients without DIC 50
5.7 Hemostatic Markers in Solid Cancer Patients without DIC 51
5.8 Frequency of DIC in Solid Cancer Patients 52
5.9 Clinical Complications in Solid Cancer Population 53
5.10 Comparison of Laboratory Findings between Solid Cancer Population with DIC and without DIC 54
5.11 Comparison of Risk Factors between Solid Cancer Population with DIC and without DIC 55
5.12 Comparison between Complications in Solid Cancer Patients with DIC and without DIC 56
5.13 Epidemiologic Data in Patients with Hematological Malignancies in Selected Articles 57
5.14 Type Of Cancer in the Population with Hematological Malignancies . 58
5.15 DIC Diagnostic Criteria Used in Different Studies 59
5.16 Global Coagulation Tests in DIC Patients 60
5.17 Hemostatic Markers in DIC Patients 61
5.18 Global Coagulation Tests in Non-DIC Patients 62

5.19 Hemostatic Markers in Non-DIC Patients 63
5.20 DIC Frequency in Patients with Hematological Malignancy 64
5.21 Complications in Patients with Hematological Malignancies 64
5.22 Comparison between laboratory findings in DIC+ and DIC- patients 65
5.23 Comparison between Risk Factors in DIC+ and DIC- Patients: 67
5.24 Comparison between Complications in DIC and non DIC Patients . . . 67
5.25 Diagnostic Criteria for DIC Established by the Japanese Ministry of Health and Welfare 68
5.26 Patients' Characteristics in the Selected Study 69
5.27 Patients' Distribution According to the Underlying Disease 69
5.28 DIC Diagnostic Criteria Used in the Selected Study 70
5.29 Patients Diagnosed with non-DIC and DIC by the JMHW Scoring System 70
5.30 Comparison between the use of global coaguation tests and JMHW scoring system to diagnose DIC 71
5.31 Study Characteristics 72
5.32 Patients' Distribution According to the Type of Hematological Malignancy 72
5.33 DIC Diagnostic Criteria Used in the Selected Study 72
5.34 Patients Diagnosed with non-DIC and DIC by the JMHW Scoring System 73
5.35 Comparison Between the Use of Global Coagulation Tests and JMHW Scoring System to Diagnose DIC 74
5.36 Patients' Characteristics 75
5.37 Different Underlying Diseases in the Studies 75
5.38 Diagnostic Rate for DIC Patients: 76
5.39 Concordance Rate between Scores 77
5.40 Prognostic Values of Scoring Systems: 78
5.41 Overt DIC and Modified Diagnostic Criteria for Non-Overt DIC to Detect DIC or Pre-DIC State 80
5.42 Diagnostic Criteria for overt DIC and non-overt DIC by ISTH and Modified non-overt ISTH 81
5.43 Study Characteristics and Design 82
5.44 Distribution of Population according to Underlying Diseases 82
5.45 Diagnostic Criteria for non-overt and overt DIC 83
5.46 Patients Diagnosed with non-DIC, non-overt DIC and DIC 83
5.47 Death Rate in non-Dic, non-overt DIC and overt DIC Patients 84
5.48 Sensitivity and Specificity for Death of Scoring Systems in non-overt DIC Patients 85
5.49 Patients' Characteristics 86
5.50 Patients' Distribution according to their Cancer Type 86
5.51 Hematimetric Parameters of Selected Patients 86
5.52 Global Coagulation Findings in the Selected Patients 87
5.53 Specific Markers Values in the Selected Patients 87
5.54 Distribution of Patients according to Score Values 87
5.55 Distribution of Patients according to the Abnormal Laboratory Findings 88
5.56 Distribution of Patients Based on the Presence or Absence of Non-overt DIC 88
5.57 Relation between Score 3 Values and Score Parameters 89
5.58 Correlation between Score 3 Values and Laboratory Findings 89
5.59 Correlation between Score 3 Values and FDP Levels 90
5.60 Relation between Score 3 Values and Complications 90

5.61 Relation between Score 3 Values and Risk Factors 90

A.1 Modified diagnostic criteria for DIC established by the Japanese Ministry of Health and Welfare 95
A.2 Modified Diagnostic Criteria for non-overt DIC proposed by Wada et al. 2012 96

List of Abbreviations

DIC	**D**isseminated **I**ntravascular **C**oagulation
t-PA	**T**issue **p**lasminogen **a**ctivator
tPAIC	**t**issue **p**lasminogen **a**ctivator **i**nhibitor **c**omplex
PPIC	**p**lasmin **p**lasminogen **i**nhibitor**c**omplex
AT	**a**ntithrombin
AVK	**a**nti **v**itamin **K**
D-D:	**D-d**imers
Elisa	**e**nzyme **l**inked **i**mmunoad **s**orbent **a**ssay
F1 + 2	**f**ragments **1** + **2** of prothrombin
FII:	**f**actor **II** (prothrombin)
FIIa	**a**ctivated **t**hrombin
FIX	**f**actor **IX**(antihemophilic factor B)
FPA	**f**ibrino**p**eptide **A**
FPB	**f**ibrino**p**eptide **B**
TF	**T**issue **F**actor
FV	**f**actor **V** (Leiden)
FVII	**f**actor **VII** proconvertine
FVIII	**f**actor **VIII** (antihemophilic factor A)
FX	**f**actor **X** (Stuart factor)
aFX	**a**ctivated **f**actor **X**
FXII	**f**actor **XII** (Hageman factor)
WBC	**w**hite **b**lood **c**ell
GP	**g**lyco**p**rotein
LMWH	**l**ow **m**olecular **w**eight **h**eparin
UFH	**unf**ractionated **h**eparin
INR	**I**nternational **n**ormalized **r**atio
ISTH	**I**nternational **S**ociety on **T**hrombosis and **H**aemostasis
IV	**i**ntra**v**enous injection
JAAM	**J**apanese **A**ssociation for **A**cute **M**edicine
JMHW	**J**apanese **M**inistry of **H**ealth and **W**elfare
KHPM	**h**igh **m**olecular **w**eight **k**ininogen
PLT	**p**latelet **c**ount
XDP	**C**rosslinked**f**ibrin**d**egradation**p**roducts
PAI-1	**t**issue **p**lasminogen **a**ctivator
PAP	**p**lasmin-**a**nti**p**lasmin
PC	**p**rotein **C**
APC	**a**ctivated **p**rotein **C**
FDP	fibrinogen/**F**ibrin **d**egradation **p**roducts
PS	**p**rotein **S**
APS	**a**ctivated **p**rotein **S**
rFVIIa	**R**ecombinant **a**ctivated **F VII**
t-PA	**t**issue **p**lasminogen **a**ctivator
rt-PA	**r**ecombinant **t-PA**

TAFI	**t**hrombin **a**ctivatable **f**ibrinolysis **i**nhibitor
TAT	**t**hrombin-**a**nti**t**hrombin
APTT	**a**ctivated **p**artial **t**hromboplastin **t**ime
TFPI	**t**issue **f**actor **p**athway **i**nhibitor
TM	**t**hrombo**m**odulin
TNF	**t**umor **n**ecrosis **f**actor
PT	**p**rothrombin **t**ime
TT	**t**hrombin **t**ime
TxA2	**t**hrombo**x**ane **A2**
UK	**u**ro**k**inase
u-PAR	**u**rokinase receptors
VWF	**v**on **W**illebrand **F**actor
FFP	**F**resh **F**rozen **P**lasma
PCC	**P**rothrombin **C**omplex **C**oncetrate
sTM	**s**oluble **t**hrombo**m**odulin
CNS	**c**entral **n**ervous **s**ystem
PIC	alpha 2-**p**lasmin **i**nhibitor-plasmin **c**omplex
ALL	**a**cute **l**ymphoblastic **l**eukemia
AML	**a**cute **m**yeloblastic **l**eukemia
CML	**c**hronic **m**yeloid **l**eukemia
MDS	**m**yelo**d**isplastic **s**yndrome
NHL	**n**on-**h**odgkin **l**ymphoma
HM	**h**ematological **m**alignancies
SC	**s**olid **c**ancer

Kahina; I dedicate this humble work to my parents, my brother and my partner that were a support for me through these years. I also dedicate this work to my dear friends and co-workers with whom I achieved these final steps, our graduation project. To my closest friends, from childhood and high school, that were and still are a major part of my life.

Chaima; First of all, I would like to thank Almighty God for giving me the strength and courage to carry out this modest work. I dedicate this work To my one and only mom thank you for all your effort your endless support and love wthout you I wont' be here, I love you to the moon and back. For my sisters Malak and Nour El Houda and brother Sif Eddine Mostapha you were always by my side supposting me and carring for me thank you For my second mom Aicha, you're the most carring person I ever known For Khaled and Amina thank you for your love and support. For my adorable niece Aridj and nephews Moncef and Moutaz. For my besties Tamtam , Sihem, awesomeness, Kahiii, Khadidja, Meriem, Chaima, Assia, Selma Djaoubi ,FfatimaZzohra Chemmoum thank you for been always there. For Khadoudj Azzouzi, the girl on fire I love you, you were always carring for me thank you. For my HADGER, my other half, thank you for been a home to me during this 6 years. For my teammates my sisters I'm glad that I had the chance to work with such amazing souls i love you. last but not least, I would like to express my warmest thanks to all those who have helped me , who supported and encouraged me and to those whom I love.

Khadoudj; For the man who raised me, who developed me and support me all the way ,without you I wouldn't achieve a thing all my respect and sincere love to you my father For the woman, who did not have the chance to see me graduate, to see her little girl realize her dream, God bless you, you give me the value of learning and the value of science, to my mother. For my sister khaoula , my second mother, who never stopped watching for me, encouraging and supporting me during my studies, may God protect you and give you all the happiness that you deserve . My brother aimen ,you have been always with me you and by my side thank you . For my butterflies kahi, meriem , khadidja, Fatima, hadjer, nesrine ,siham ,amira, im not going to forget those days together thanks for the love and care I wish you all the success, happiness and the joy during your lifes. For my best friend , my sister ,my soul mate ,chaima thank you for being with me for those good days for the support and for the courage you are the wonderful thing that happened to me during my universery life all the luck and success in your life For my trinomial Kahina and Chaima, the best people I have worked with, my colleagues and my friends, thank you for your understanding, patience and moral support. . . .

Introduction

Disseminated intravascular coagulation (DIC) is a complex pathology that is often associated with sepsis, trauma, malignancies and obstetrical calamities Levi 2007a; Gando et al. 2016. It is defined by The Scientific and Standardization Committee (SSC) on DIC of the International Society on Thrombosis and Haemostasis (ISTH) as: "an acquired syndrome characterized by the intravascular activation of coagulation with a loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction" Taylor et al. 2001.

DIC is known to complicate many cancers, especially hematological ones. Its clinical manifestations can go from asymptomatic to fulminant, and it is often associated with poor prognosis.

In order to improve patients' outcome, scoring systems that compile different laboratory tests (global and specific) were developed, but researches that aim to enhance diagnostic and prognostic capacity of DIC are still ongoing.

The real challenge today is to find a gold standard that can diagnose DIC with any underlying disease, in an early stage, and that is easy to use in emergency situations. So, how has diagnosis of DIC evolved during the last few years? And where are we today with this pathology?

This work is divided into two parts: a review of the literature and a practical section. The review of the literature aim to gather information about:

- The frequency of DIC in patients with cancer (solid cancers and hematological malignancies).
- Laboratory findings (global and specific tests) in cancer patients with and without DIC.
- Complications that occur in cancer patients with and without DIC.
- Risk factors that may be associated with cancer patients having DIC.

And to :

- Explore the evaluation of global tests accuracy compared to scores in the diagnosis of DIC.
- Compare between different scoring systems in the diagnosis of DIC and their capacity of predicting death in DIC patients.
- Compare between different scores in predicting death in patients with non-overt DIC

The practical section aim to explore:

- The occurence of non overt DIC in the selected patients (solid cancer).
- Laboratory changes in the selected patients.

- Score values found in the selected patients according to the modified diagnostic criteria for non-overt DIC Wada et al. 2012.
- Clinical manifestations that may be associated with higher score values.
- Risk factors that may be associated with higher score values.

Chapter 1

Physiological Recall

1.1 Haemostasis

Haemostasis is a process that prevents haemorrhage by arresting and keeping the blood within the damaged vessel walls. It is a complex process that is contingent on the complex interaction of platelets, plasma coagulation cascades, fibrinolytic proteins,blood vasculature and cytokine mediators.

1.2 Phase 1: Primary Haemostasis

1.2.1 Vasoconstriction

Vascular spasm occurs whenever there is an injury or a damage in the blood vessels. This will trigger a vasoconstriction localized to the injured area; which could eventually stop the blood flow Periayah et al. 2017.

1.2.2 Platelet Plug Formation

Following vasoconstriction, exposed collagen from the damaged surface will encourage platelets to adhere, activate and aggregate to form a platelet plug, sealing off the injured area Periayah et al. 2017.

1.2.3 Platelet Adhesion

At sites of vessel injury, the adhesion process involves the interaction of platelet glyco-protein Ib (GPIb), connective tissue elements that became exposed (e.g., collagen), and plasma von Willebrand factor (vWF) as an essential cofactor Hanson and Tucker 2007.

1.2.4 Platelet Activation

Platelet cell activation is characterized by two main phenomena, their change and their metabolic activation. These are active processes requiring energy, in the form of ATP, and the intracytoplasmic availability of calcium ions (Ca++). The intracytoplasmic granules fuse with the open canalicular system and release their content. This phenomenon of platelet secretion, releases many proaggregating substances (ADP, fibrinogen, serotonin) and procoagulants (Factor V, VWF, fibrinogen) or vasomotors (serotonin, NO, TXA2) contributing to the amplification of the primary haemostasis process and creating the favourable conditions for plasma coagulation. Another key phenomenon taking place during the platelet activation phase is the *membrane "flip-flop" phenomenon which allows phospholipids negatively charged, including the phosphatidylserine, to exteriorize and become available for coagulation factor binding

vitamin K-dependent; thereby, amplifying considerably the enzymatic processes of the coagulation cascade Hanson and Tucker 2007.

1.2.5 Platelet Aggregation

ADP and traces of thrombin initially produced through the early stages of coagulation are the major agonists of platelet aggregation, which is then amplified by other substances such as TXA2, adrenaline or serotonin.

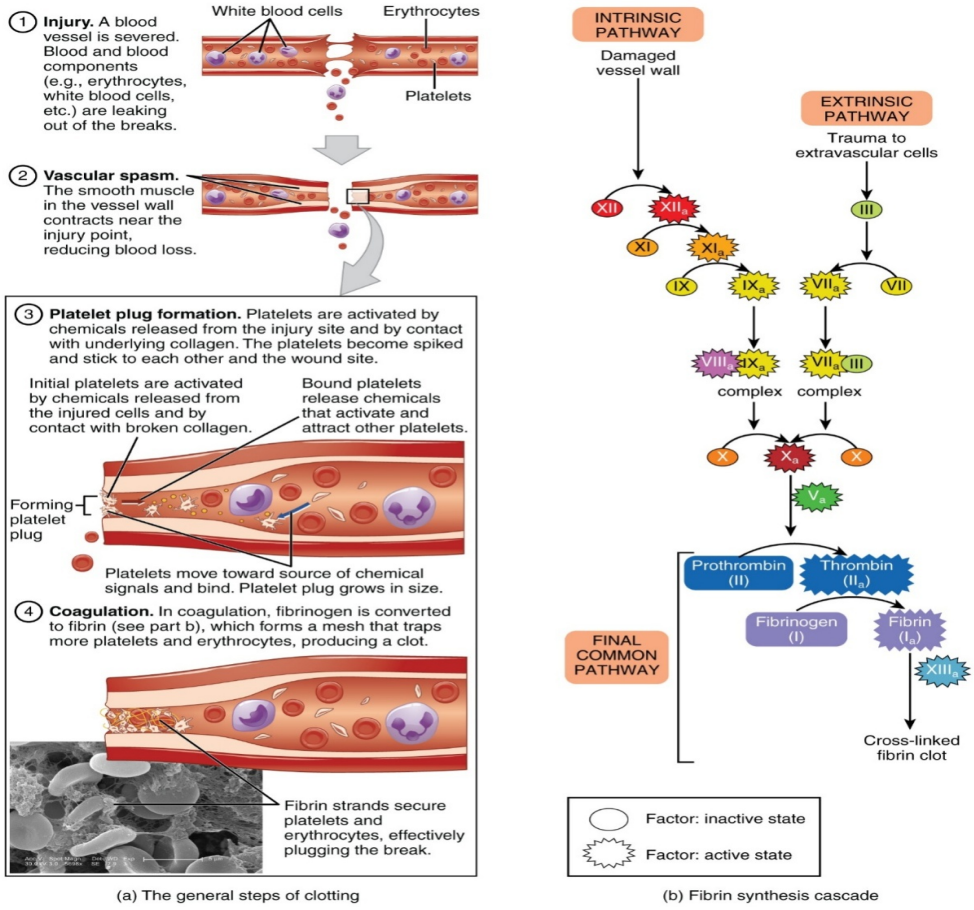

Figure 1.1: Haemostasis Pathway learning objectives 2020

1.3 Phase 2: Coagulation Physiology

1.3.1 Coagulation Pathway

1. **Coagulation Factors**
   According to their activity or their mechanism of synthesis, coagulation factors are classified as contact system factors, vitamin K-dependent factor or Coagulation co-factors table1.1.

2. **Coagulation Steps**

   Initiation of Coagulation: In a vascular injury, the tissue factor present in the outer tunic of the vessel is brought into contact with the circulating blood which contains both factor VII and traces of factor VIIa. The exposed tissue

Factors	Concentration Factors ($\mu g\,mL^{-1}$)	Half-Life(Hours)	Remark
Fibrinogen	3000	72-108	-
Factor II	70-90	-	Vitamin K dependent factor
Factor V	15-36	-	Cofactor
Factor VII	0.5	5	Vitamin K dependent factor
Factor VIII	0.1	15	Cofactor
Factor IX	5	24	Vitamin K dependent factor
Factor X	10	30-50	Vitamin K dependent factor
Factor XI	4-6	52	-
Factor XII	29-40	-	Factor of the contact system
Factor XIII	10	9 days	-
KHPM	70-90	-	Cofactor of the contact system

Table 1.1 Coagulation Factors Harif 2015

factor captures both factor VII and factor VIIa which results in immediate self-activation of factor VII. The complex (tissue factor/VIIa) then activates the factors IX and X fixed in proximity of the membrane surfaces. This pathway of coagulation activation, which is paramount, is referred to as the exogenous pathway.

3. **Thrombin Formation and Amplification of the Process**
   Factor IXa activates its substrate factor X, and Xa activates its respective substrate factor II on the surface of activated platelet membranes. At the end of this chain of reactions, the first molecules of thrombin are formed. Thrombin immediately amplifies its own formation:

   - Thrombin stimulates the platelets passing nearby by attaching themselves on its receiver (PAR1) and by splitting it. This allows the recruitment and activation of new platelets and increases platelet thrombus for greater exposure of membrane aminophospholipids.
   - It also activates co-factors VIII and V: factor VIIIa accelerates the activation of factor X by factor IXa; factor Va accelerates the activation of factor II by factor Xa.
   - It is also able to activate factor XI, strengthening the reactions that lead to its own production.
   - Thrombin can also activate cell types other than platelets, especially leukocytes and vascular cells.

4. **Activation of Factor XI and Contact Phase**
   Factor XI is activated by thrombin and will activate the factor IX, which leads to a succession of enzymatic reactions described above and enhances thrombin production. But There is another way of activating factor XI (the initiating of coagulation) which is of minor importance compared to coagulation initiation by tissue factor. It is the consequence of the contact of plasma proteins with the sub-endothelium, involving proteins of contact phase: factor XII and prekallikrein, which are zymogenic serine proteases, and the high molecular weight kininogen (HMWK) which acts as a cofactor (figure1.2).

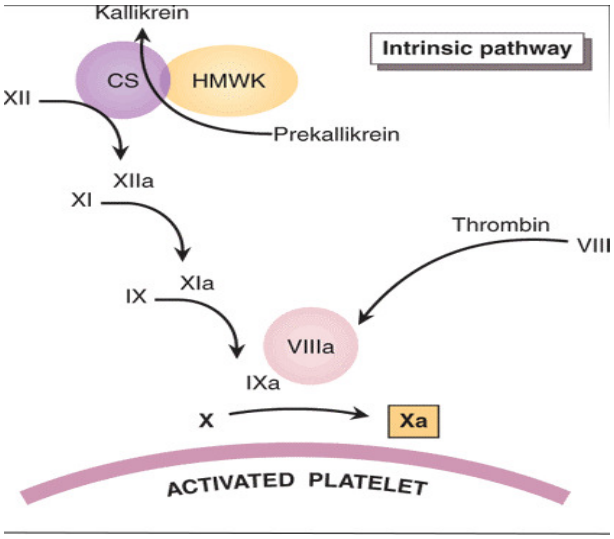

Figure 1.2: Another way of Activation of Factor XI via Contact Protein (Robert S. Hillman, Kenneth A. Ault, Michel Leporrier 2011)

Prekallikrein and Factor XI circulate in the blood binding to the HMWK. In the case of endothelial lesions, factor XII and HMWK (and through it, prekallikrein and factor XI) bind to the sub-endothelium. Prekallikrein is then transformed into kallikrein by a vascular wall protease. Kallikrein in turn activates factor XII, which in turn activates factor XI. The factor XIIa amplifies the process by retroactively activating the pre-kallikrein.

The role of this activation pathway (called the endogenous) in coagulation is minor, and its deficit, even if severe, in factor XII, pre-kallikrein or HMWK does not lead to an increased risk of haemorrhage.

1.3.2 Fibrin Clot Formation

When the concentration of formed thrombin hits a certain level, it converts soluble fibrinogen to fibrin insoluble. Fibrin forms a solid envelope around the aggregate of platelets to achieve clotting.

1. **Fibrino-formation Steps**

   - *Proteolysis of fibrinogen by the thrombin*: Thrombin cleaves off two sets of peptides, fibrinopeptides A and B (E domain), from the amino terminal ends of the Aα (Arg 18-Gly) and Bβ (Arg 16-Gly) chains, that leads to the formation of fibrin monomers Guillin 2001.
   - *Polymerization of fibrin*: After liberation of fibrinopeptides A and B, domains D and E expose their binding sites. The E central domain of one monomer interacts with the D domain of another monomer. These non-covalent bonds are called contact sites D-E. Fibrin strands are formed and D-D contacts are also established 1.3 Harif 2015.
   - *Fibrin stabilization*: Unstable fibrin polymers must be stabilized by factor XIIIa. Activation of factor XIII is achieved by thrombin, and this activation is regulated by the presence of calcium and fibrin which serves as a cofactor Guillin 2001.

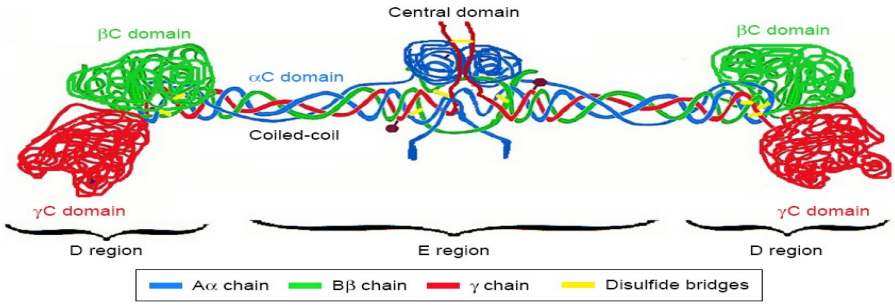

Figure 1.3: Fibrinogen Structure (Vaez-ghaemi et al. 2017)

Factor XIIIa is a transglutaminase. It stabilizes the clot by creating c-glutaminelysine covalent bonds between the c-chains of two adjacent fibrin monomers, and between chains of several monomers 1.3.

This linkage leads to the formation of a very strong fibrin clot. Factor XIIIa could also intervene by docking the fibrin clot to the subendothelium such as fibronectin and could also, by binding a2-antiplasmin to fibrin, delay clot destruction by plasmin until the tissue is repaired.

1.4 Regulation of Coagulation

1.4.1 Serpins

Serine protease inhibitors[or serpins are single-stranded proteins that have a reactive centre in their N-terminal region that allows them to behave as a suicide substrate for the target enzyme with which irreversible complexes are formed. The serpins that control coagulation are:

1. **Antithrombin**
   It is one of the most potent inhibitors of plasma clotting by inhibiting thrombin and other coagulation factors (the factors Xa, IXa, XIa, and XIIa). It is synthesized by the liver, lungs, spleen, and endothelial cells of the vascular walls. Heparin (endogenous and exogenous) is a cofactor of antithrombin III and potentiates its effects Harif 2015.

2. **Second Heparin Cofactor**
   It is another serpine capable of inhibiting thrombin, synthesized by the hepatocytes. It inhibits thrombin (but none of the other coagulation or fibrin proteases). Its action is potentiated by another glycosaminoglycan Harif 2015.

3. **Protein C System**
   Protein C, a vitamin K-dependent serine protease that needs a cofactor, protein S, to act, will exert its anticoagulant effect by inactivating, via proteolysis, factors Va and VIIIa. Protein C is activated by thrombin bound to thrombomodulin (an endothelial cell membrane receptor) Philippe Codine, Nelly Kotzki 2005.

4. **Inhibition of the Tissue Factor Pathway (TFPI)**
   TFPI is present in both circulating blood and bound to glycosaminoglycans in the vascular wall Guillin 2001.

   The role of TFPI becomes important after the generation of small quantities of the Xa facto on which TFPI is fixed. A quaternary complex Xa-TFPI-VIIa- TF

is then formed. The VIIa-Tissue Factor complex is inhibited, thereby blocking the production of Xa and IXa.

1.4.2 Other Inhibitors

- *α-2 Macroglobuline* which is not a serpine, is involved in approximately 25% of thrombin inhibition Guillin 2001.
- *α-1 Antitrypsine and C1 inhibitor*: (serpin) is capable of inhibiting some of the coagulation enzymes, but their role in vivo is insignificant Guillin 2001.

1.5 Phase 3: Fibrinolysis

Fibrinolysis is a physiological system that results in the lysis of a fibrin clot. This system allows a balance with coagulation. Its role is to dissolve a constituted thrombosis and to prevent fibrin accumulation.

1.5.1 Fibrinolysis Actors

1. *Plasminogen*, the precursor of plasmin, is a plasma glycoprotein of hepatic synthesis, comprising in its structure 5 loops called kringles Lasne et al. 2006.
2. *Plasmin* is a serine protease that has the ability to split fibrin into fibrin degradation products that are soluble in plasma Kathleen M Botham, Anthony Weil, Victor W Rodwell, Peter J Kennelly 2017.
3. *Plasminogen activators*:
   - *t-PA (Tissue Plasmin Activator)* is the main activator. It is synthesized by endothelial cells and has a high affinity for fibrin. Its action is 1,000 times greater on plasminogen adsorbed to fibrin than on plasminogen free Harif 2015.
   - *Urokinase* is another activator but of lesser importance. This activator is synthesized by endothelial cells, monocytes, and macrophages in the form of pro urokinase and has no direct affinity for fibrin Harif 2015.

1.5.2 Fibrinolysis Steps

1. **The formation of Plasmin**
   Free plasminogen, as well as t-PA released from endothelial cells by adrenergic stimulation during venous occlusion or trauma, binds to fibrin. On the other part, activation of the contact system will also activate uPA.

   Fibrin plays a major role in the catalysis of plasminogen activation into plasmin. The first traces of plasmin will also act on plasminogen to transform it into plasmin (self-amplification phenomenon) Harif 2015.

2. **The Formation of Fibrinolysis Products**
   Plasmine degrades fibrin into soluble degradation products (Figure 1.5) that are released into the circulation.

   It is also capable of acting on fibrinogen, which is referred to as fibrinogenolysis, and on coagulation factors V and VIII. The action of plasmin is progressive. Initially there is a release of fragments of the chains Aα and Bβ giving rise to

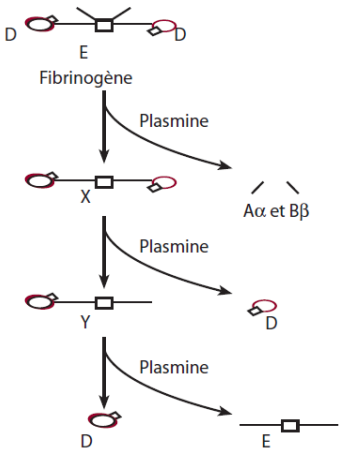

Figure 1.4: Fibrignogen Degradation by Plasmin Harif 2015

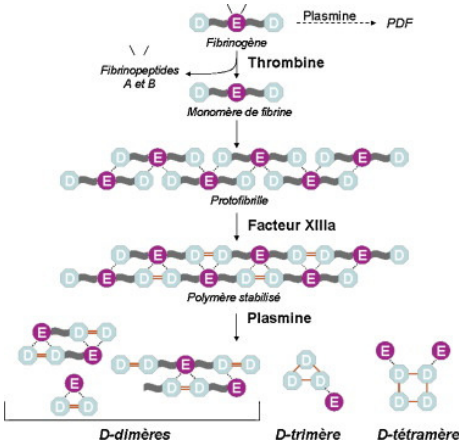

Figure 1.5: Fibrinogen Degradation Nougier and Marijon 2012

coagulable products called X fragments. New cleavages give rise to fragments D and Y then to fragments E Harif 2015.

The action of plasmin on fibrin is more laborious because of the links between the molecules. Fibrinolysis gives rise to fragments of various sizes, the smallest of which are the D-Dimers, which come from the D-domains linked by covalent bonds developed by factor XIIIa during the fibrin stabilisation reaction. Fibrin or fibrinogen degradation products (PDF) consist of early (X and Y) and late (D and E) products, physiologically this process remains localized Harif 2015.

3. **Fibrinolysis Inhibitors**

1. *α-2 Antiplasmin* is the main protein with antiplasmin activity; it is a glycoprotein synthesized by liver cells that neutralize circulating non-fibrin-bound plasma plasmin.

2. *PAI (Plasminogen Activator Inhibitor)*:

   - **PAI-1(type 1 or PAI-1)** is the major plasminogen activator inhibitor (PAI); it is a glycoprotein synthesized by the endothelial cell that inhibits t-PA and u-PA, and is released during platelet activation.
   - **PAI-2(type 2 or PAI-2)** is another synthesized inhibitor through the placenta during pregnancy Professeur and Assistant 2004.

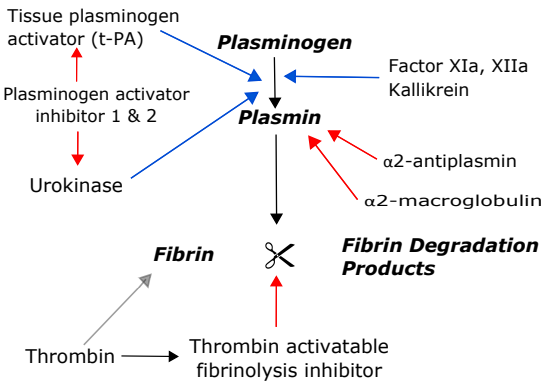

Figure 1.6: Fibrinolysis by Formation of Plasmin, Inhibitors and Activators of Fibrinolysis Process (*Fibrinolysis*)

Chapter 2

Exploration of Haemostasis

2.1 Primary Haemostasis

2.1.1 Platelet Enumeration

When faced with the onset of haemorrhagic syndrome, platelet count looking for a thrombocytopenia precedes any other test. Recall that the normal platelet count is between 150 and 400 $10^9 L^{-1}$. A rate higher than 30 $109 L^{-1}$ does not pose a risk of spontaneous bleeding. The discovery of thrombocytopenia requires a control on blade and a new numbering on citrated anticoagulant. Ethylene diamine tetraacetic (EDTA) usually used can generate in vitro platelet agglutination, thereby reducing the particle count of the automaton Professeur and Assistant 2004.

2.1.2 Bleeding Time

This is the cornerstone of exploring primary haemostasis, and it is defined as the time required for spontaneous cessation of bleeding caused by a small superficial cut. It explores the different elements contributing to primary haemostasis, i.e. platelets, the vascular wall and the VWF. This test, which is performed classically, according to the method initially described by Ivy, by a superficial skin incision in the forearm under a constant pressure of 40 mmHg. Under these conditions, the bleeding time (BT) is between 4 and 8 minutes Professeur and Assistant 2004.

2.1.3 The Time of Occlusion

Also known as the PFA100 test, reproduces the physiological conditions of primary haemostasis. The formation of a platelet nail on a collagen support in the presence of an activator (ADP or epinephrine), leads to the occlusion of the capillary tube under high shear forces Harif 2015.

2.1.4 Study of Membrane Receptors by Flow Cytometry

Flow cytometry (FC) is a technique of rapidly measuring specific characteristics of many different cells such as platelets, measuring the cell size, and granularity. FC analysis of platelets may offer information on their functional status in vivo, and this technique encompasses multiple assays for several purposes such as the assessment of the activation state (platelet membrane-associated IgG), evaluation of thrombopoiesis, diagnosis of specific disorders, and antiplatelet agent monitoring Priora 2015.

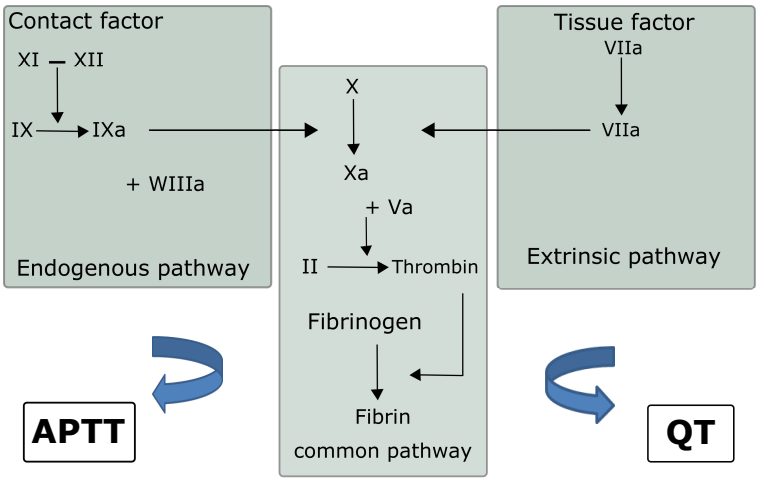

Figure 2.1: In vitro coagulation testing. Activated partial thromboplastin time (APTT) explores endogenous and common pathway factors; prothrombin time (PT) explores tissue factor VII and common pathway factors (Revel and Doghmi 2004)

2.2 Exploration of Coagulation

TCA and Prothrombin Time (PT) are the two screening tests universally used to explore the different phases of coagulation. The specific coagulation factor assays, in search of an isolated deficiency, is performed based on the results of the previous tests.

2.2.1 Activated Partial Thromboplastin Time (APTT)

The APTT explores contact factors (factors XII, XI) and factors IX, VIII, X, V, II and fibrinogen. The normal time depends on the activators and the cephalin used by each laboratory, and ranges from 30 to 40 seconds. The APTT of a given patient should be compared to the laboratory control APTT, and a time 6-10 seconds above the control is considered pathological Professeur and Assistant 2004.

2.2.2 Prothrombin Time

Prothrombin time (PT) corresponds to the coagulation time of a decalcified and displaced plasma in the presence of thromboplastin, a source of tissue factor, and calcium.

PT explores factor VII, extrinsic pathway factor, and common pathway factors X, V, II and fibrinogen. It is between 10 and 13 seconds depending on the thromboplastin used, and is expressed as a percentage of a plasma pool calculated according to a reference curve.

It is then called prothrombin activity (PA). The normality is between 70 and 100% 2.1 Professeur and Assistant 2004.

2.2.3 Specific Dosages of Coagulation Factors

They must be requested in response to abnormal screening tests (APTT or TQ) for an acquired or constitutional deficiency in one or more of the clotting factors. It is possible to dose each of the coagulation factors individually. The principle is based on the ability of the plasma to test and correct the clotting time of a plasma that is specifically deficient in one factor to be measured Professeur and Assistant 2004.

2.2.4 Fibrinogen Assay

Fibrinogen testing is performed by a variety of methods its rate is normally included between 2 and 4g L^{-1} Professeur and Assistant 2004.

2.2.5 Determination of coagulation inhibitors:

In different pathologies, we are more and more often led to measure coagulation inhibitors to try to understand the reason of repetitive thrombosis, all inhibitors can be measured by functional or antigenic method: Antithrombin, protein c, protein s Philippe Codine, Nelly Kotzki 2005.

2.3 Exploration of Fibrinolysis

2.3.1 Global Tests

Euglobulin lysis time: it represents the lysis time of a plasma or whole blood clot and it takes 48 to 72 hours. In order to make the test faster, fibrinolysis inhibitors are extracted by precipitation in an acidic medium. The precipitate containing the plasminogen and its activators is coagulated. Its lysis should not normally take place in less than 1.5 hours. In case of hyperfibrinolysis the time is shorter Harif 2015.

2.3.2 Determination of Fibrinolysis Factors

Rarely indicated, plasminogen, α-2 antiplasmin, PAI and tPA may be assayed. This assay is reserved for specialized laboratories and its indications are limited Harif 2015.

Chapter 3

Disseminated Intravascular Coagulation

3.1 Definition

Disseminated Intravascular Coagulation (DIC) is described as a systemic thrombohaemorrhagic disorder Bick 2003, it results in an excessive activation of coagulation away from the site of the damaged endothelium, which represents the "disseminated" picture Thachil 2016.

It is considered as a syndrome characterized by over activation of intravascular coagulation, accompanied by consumption of coagulation factors Urge and Strojil 2006, with an abnormal fibrinolytic state Thachil 2016; the variations of balance between these mechanisms will influence the clinical picture of the patient.

3.2 Epidemiology

Haemostatic derangements have long been observed in patients with cancer and that because of the capacity of the malignant cells to release procoagulant materials in the systemic circulation Bick 1992a. DIC is considered to be one of the most problematic hematological complications in cancer patients; however, DIC in cancer has generally a more chronic presentation and is likely to have a more gradual evolution Levi 2009. The incidence of DIC in consecutive patients with solid tumors was found to be 7% in patients with acute promyelocytic leukaemia. DIC may be diagnosed in more than 90% of patients at the time of diagnosis or after initiation of remission induction Sallah et al. 2001; Tiziano Barbui 2001. According to Sallah et al. 2001 study, the factors that are relied to the occurrence of DIC in cancer patients are the gender, the age, the breast tumor and the presence of necrosis in the tumor cells Sallah et al. 2001. DIC is the most common coagulation complication observed in prostate cancer patients; in addition, the incidence of DIC in prostate cancer is reported to be between 13 and 30%. However, the clinical signs of DIC are apparent in only 0.4-1.65% of patients with prostate Ruffion et al. 2000.

In general terms, disseminated intravascular coagulation is observed in about 1% of all hospital admission Matsuda 1996, and according to the ISTH (International Society on Thrombosis and Heamostasis) and JAAM (Japanese Association for Acute Medicine), the occurrence of DIC in sepsis patients is 30%-51%, and is about 45% for patients after trauma or major surgery Gando et al. 2016.

3.3 Pathophysiology

3.3.1 Risk Factors for DIC

Disseminated intravascular coagulation is an acquired disorder that occurs in a wide variety of clinical conditions, the most frequent of which are listed in Table 5.11, and the important ones will be discussed further.

Conditions	Examples	Impact of precipitating conditions
Severe infectious diseases	Gram-positive or -negative organisms, malaria, hemorrhagic fevers	Thrombosis may contribute to organ failure (eg acute kidney failure)
Malignancy	Solid tumors (eg adenocarcinomas), Acute promyelocytic leukemia or monocytic leukemia	Primarily thrombotic consequences/ VTE, severe thrombocytopenia and factor deficiency may lead to bleeding
Trauma	Multitroma Brain injury Burns	Primary feature is bleeding, followed by thrombosis
Obstetrical complications	Abruptio placentae Amniotic fluid embolism	Profuse bleeding with thrombotic complications
Vascular malformations	Kasabach-Merrit syndrome Giant hemangiomas Other vascular malformations Large aortic aneurysms	Bleeding primarily with severe throbocytopenia and hypofibrinogenemia
Severe immunologic reactions	Transfusion reaction	-
Heart stroke	-	Thrombotic features more than bleeding
Post-cardiopulmonary resuscitation	-	Thrombosis is a greater risk than bleeding

Table 3.1 Clinical Conditions most Frequently Associated with DIC Facts 2020

1. **DIC and Sepsis**

   In sepsis, the causative agent and the associated inflammatory response drive fibrin formation and deposition by several simultaneously acting mechanisms Balwinder Singh 2014.

2. **DIC and Trauma**
   Trauma patients are susceptible to an early development of coagulopathy, and the most severely injured patients are coagulopathic on hospital admission. The incidence of DIC in patients with severe trauma and systemic inflammatory response syndrome can be as high as 70% "Disseminated Intravascular Coagulation in Trauma Injuries".

3. **DIC and Obstetrical Pathologies**
   Normal pregnancy and childbirth are known to be associated with marked

changes in the coagulation and fibrinolytic systems, which convert pregnancy and child birth into a hypercoagulable state vulnerable to a spectrum of disorders ranging from venous thromboembolism to DIC Kramer et al. 2002.

4. **DIC and Liver Failure**
   The extent of coagulation abnormalities in liver disease patients depends on the intensity of the hepatocellular damage. At the early stages, despite the low production of pro- and anticoagulant proteins, mainly the vitamin K-dependent factors (factors II, VII, IX, and X, proteins C and S), a relatively normal haemostasis is maintained. In advanced cases, conversely, a wide spectrum of factor deficiencies and even disseminated intravascular coagulation (DIC) may develop Refaai 2020.

5. **DIC and Vascular Disorders**
   Large aortic aneurysms or giant hemangiomas (Kasabach-Merritt syndrome) may cause local activation of coagulation. Studies employing radiolabeled fibrinogen and platelets provided evidence that there is consumption of these factors within the vascular lesions due to intravascular clotting and excessive fibrinolysis Kramer et al. 2002.

6. **DIC and Toxic Reactions**
   Snake venom has action similar to thrombin and tends to form fibrin unlike stable fibrin molecules. This unstable fibrin polymer is vulnerable to fibrinolyis and phagocytosis by reticuloendothelial system. This imparts the property of inducing various types of coagulopathy to snake venom ranging from a simple thrombocytopenia to a full blown DIC Balwinder Singh 2014.

3.3.2 DIC Mechanisms

1. **Triggers of Fibrin Formation**
   The activation of coagulation leading to thrombin formation in DIC is mediated exclusively by tissue factor/factor VII(a) pathwayLevi 2007b. The origin of tissue factor (TF) is not completely clear Levi 2007b and it depends on the underlying conditions:

   - Pro-inflammatory cytokins can induce the expression of TF on mononuclear cells (mainly interleukin 6 (IL-6)) Levi 2007b.
   - Damaged endothelial cells resulting from various insults may also be a source of TF Gando et al. 2016.
   - Pro-inflammatory mediators, such as platelet-activating factors, can also directly activate platelets Gando et al. 2016, that will result into a further activation of coagulation. In addition, platelets, following their activation, can express P-selectin on their membrane which regulates the adhesion of platelets to leukocytes and the vascular endothelium, and also boosts the expression of tissue factor on mononuclear cells Van Noort 2002.

2. **Inhibitory Systems**
   In patients with DIC, the most important anticoagulant factors are generally reduced: antithrombin (AT), the protein C system (PC), and tissue factor pathway inhibitor (TFPI)) Levi 2007b.

   - *Antithrombin*: Besides its anticoagulant function, AT is also known to have anti-inflammatory properties by promoting the release of prostacyclin, a strong antiplatelet aggregant; it has also a role in down-regulating

P-selectin activity, as well as leukocyte activation Thachil 2016. Nonetheless, plasma levels of AT are significantly reduced during DIC due to a combination of consumption, degradation by elastase from activated neutrophils, and a lack of synthesis Levi 2007b.

- *Protein C system*: The perturbances in protein C system are of great importance in DIC's process. It has been found that decreased plasma levels of protein C are a result of impaired protein synthesis, cytokine mediated down-regulation of endothelial thrombomodulin, and a decrease in the concentration of the free fraction of protein S Levi 2007b.
- *TFPI*: Even though the relevance of TFPI has not been demonstrated yet during DIC in patients Gando et al. 2016, it has been shown that the experimental rabbits challenged with the same dose of endotoxin or tissue factor died of fulminant DIC when plasma levels of TFPI were low Thachil 2016; furthermore, the harmful effects of experimental bacteraemia in baboons seemed to be less important and vital functions improved when TFPI was administered Gando et al. 2016.

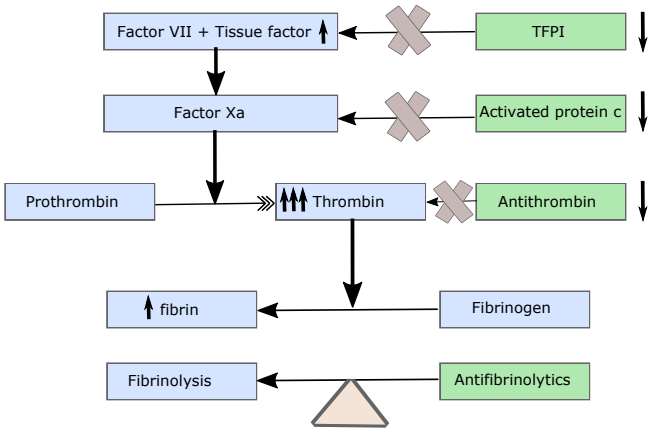

Figure 3.1: The Abnormal Haemostatic Systems in DIC
Thachil 2016

3. **Fibrinolytic System**
   Concerning the fibrinolytic system abnormalities in DIC, we can distinguish two pathways depending on the underlying conditions:

   - A hypo-fibrinolysis state: It is caused by high levels of PAI-1 released either directly by endothelial cells Dirik and Kolusarı 2019, or in response to increased t-PA plasma levels. This results into a thrombotic type of DIC Jong et al. 2013
   - A hyper-fibrinolysis state: The most important point in this situation is the time difference between the immediate t-PA release from the endothelium and later expression of PAI-1 mRNA; this leads to an extreme imbalance of these molecules Gando and Otomo 2015, and therefore severe bleeding symptoms are likely to appear.

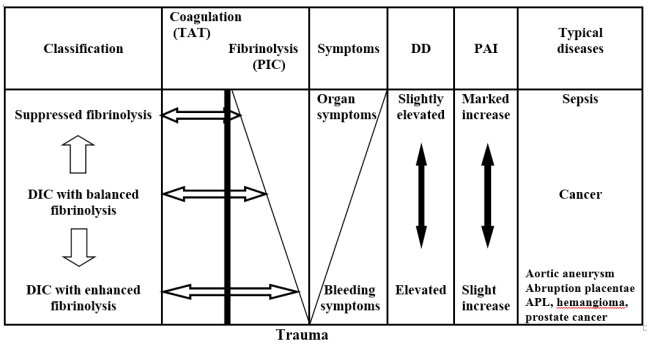

Figure 3.2: Classification of Disseminated Intravascular Coagulation Types

TAT: thrombin-antithrombin complex, PIC: plasmin-α-2 plasmin complex, DD: D-dimer,PAI: plasminogen activator inhibitor, APL: acute promyelocytic leukemia Asakura 2014

3.4 Clinical Manifestations

The clinical symptomatology in DIC is variable. We can notice two dominant presentations: the hyper-coagulable state and the hemorrhagic diathesis state; these two manifestations can overlap, and convert from one to the other as well Urge and Strojil 2006.

Severity of the clinical course of DIC is conditioned by different components: the rate of activation of coagulation, the rate of consumption of coagulation substrates and the efficiency of the fibrinolytic system; adding to that the rate of regeneration of platelets and coagulation factors by bone marrow and liver Dirik and Kolusarı 2019.

Hence, we can notice two major symptoms of DIC: bleeding symptoms and organ symptoms, that considerably worsen the prognosis when they become apparent Asakura et al. 2016.

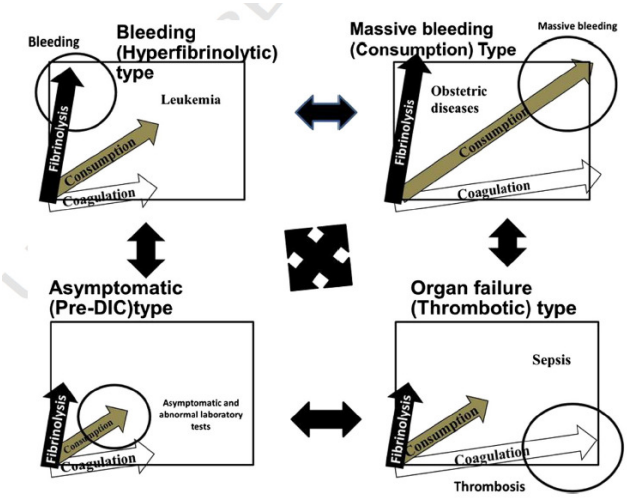

Figure 3.3: Four Types of DIC
Wada et al. 2014

3.4.1 Bleeding

Bleeding symptoms are varied; it can manifest as small petechiae as well as massive internal or external bleeding Balwinder Singh 2014.

When bleeding occurs, in the acute or the chronic form, it can cause tissue necrosis in different organs such as the skin and the kidneys, and infarcts may appear in the latter Dirik and Kolusarı 2019. Besides, hemolysis anemia due to microangiopathy, as well as hypovolemia and hypotention due to the leaking of fluid in the interstitial space may also occurDirik and Kolusarı 2019.

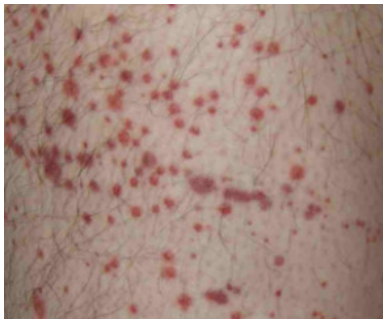

Figure 3.4: Clinical Manifestation of DIC *CM1*

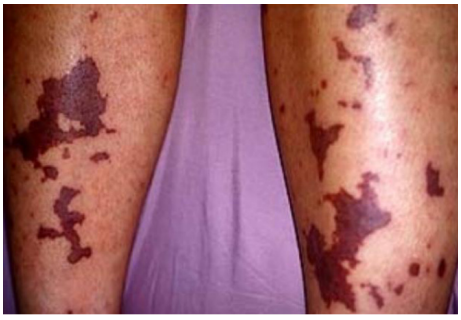

Figure 3.5: Clinical Manifestation of DIC *CM2*

3.4.2 Thrombosis

Most patients with DIC, besides having haemorrhage, also have significant diffuse thrombosis in microvascular vessels as well as large ones. These thrombotic manifestations are often responsible for end-organ damage Bick 2003, and if severe enough, may lead to organ dysfunction complications Taylor et al. 2001. Functional loss occurs in major organs due to hypoxic damage, microvascular thrombosis and bleeding Dirik and Kolusarı 2019.

3.5 Complications of DIC

DIC becomes complicated when the clinical manifestations involve functional and/or vital prognosis, or when it is associated with organ failure Dumas et al. 2006.

3.5.1 Multiple Organ Failure Syndrome (MOFS)

The Multiple Organ Dysfunction Syndrome (MODS) can be defined as "the development of potentially reversible physiologic derangement involving two or more organ systems (...), and arising in the wake of a potentially life-threatening physiologic insult" Holzheimer RG, Mannick JA 2001.

It has been found that the MODS (or MOFS) most frequently occured in patients with DIC rather than patients without DIC Dhainaut and Charpentier 2002, as an example, Asakura and al reported that in 69 patients in the intensive care unit (ICU), the mortality was about 31% in patients with MODS and non-existent in patients without MODS Asakura et al. 2001.

The MODS, according to different studies, is often caused by the formation of many microthrombi in the microvasculature which will induce hypoxia at tissue level and organ injury Asakura et al. 2001. This situation is worsened by the depletion of the inhibitory systems (AT and PC) as well as the fibrinolytic system. On the other hand, MODS seems to be improved when the latter is enhanced to solve microthrombi

Asakura et al. 2001; Dhainaut and Charpentier 2002. Also, inflammation may play a role in the induction of MODS Physicians 1998.

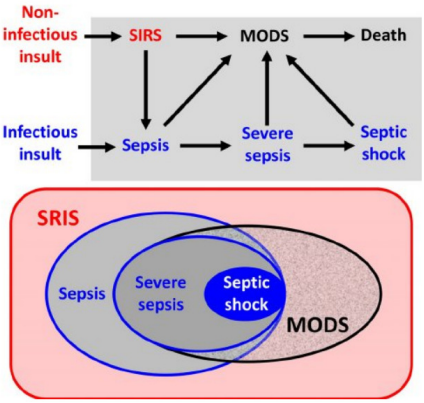

Figure 3.6: Evolution of SIRS to MODS (Du Pont-Thibodeau et al. 2014)

3.5.2 Systemic Inflammatory Response Syndrome (SIRS)

"Systemic inflammatory response syndrome (SIRS) is the clinical expression of the action of complex intrinsic mediators of the acute phase reaction" (the primary part of the systemic inflammatory response). "SIRS can be precipitated by events such as infection, trauma, pancreatitis, and surgery" Physicians 1998.

The pro-inflammatory cytokins (TNF-α, IL-1, IL-6 and IL-8) are considered to be the mediators of the inflammatory response, and the proportions of ones compared to the others vary depending on the trigger (infection, trauma...)Physicians 1998. It has been found that there is a crosstalk between inflammation and coagulation, since pro-inflammatory cytokins can activate the coagulation system by influencing the expression of TF on activated mononuclear and endothelial cells, and at the same time impair the inhibitory systems such as the fibrinolytic systems Jong et al. 2013.

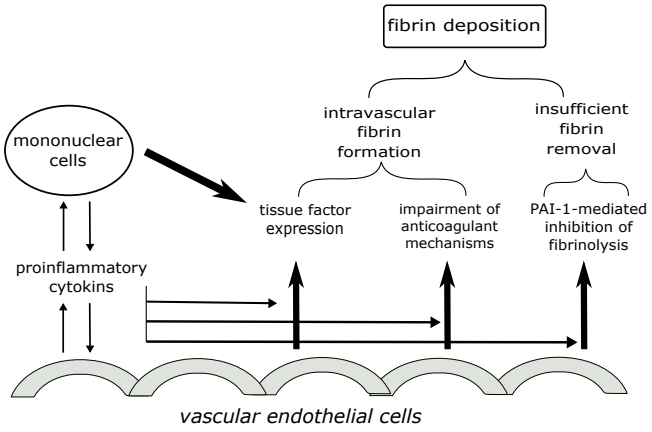

Figure 3.7: Schematic Representation of Pathogenetic Pathways in Disseminated Intravascular Coagulation during Systemic Inflammatory Response syndromes
Levi 2007b

3.6 DIC in Cancer

3.6.1 Definition of Cancer

Cancer is defined by the Merk Manual 19th edition as: "an unregulated proliferation of cells due to loss of normal controls, resulting in unregulated growth, lack of differentiation, local tissue invasion, and, often, metastasis.". It can develop in any tissue of the organism and at any age.

We can divide cancer into two categories:

1. **Solid Cancer**
   It is characterized by the formation of malignant neoplasms (solid tumors), which are abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign, or malignant (cancer). Different types of solid tumors are named according to the nature of cells that form them like sarcomas, carcinomas and lymphomas. The term solid tumor is used to distinguish between a localized mass of tissue and leukemia Thomas N. Seyfried1 and Huysentruyt 2013.

2. **Hematological Malignancies**
   It can be divided into:

   - *Leukemia*: It is a broad term for cancers of the blood cells. It usually affects the blood-forming tissue (ex. Blood marrow); it results in the production of abnormal blood cells that will enter the bloodstream, and over time, lead to replacement of normal blood elements with malignant cells. At first, leukemia was termed acute or chronic depending on life expectancy, but now it is based on cellular maturity of the targeted cells NIC 2020; Porter, R. S., & Kaplan 2011.
   - *Lymphomas*: The classification of lymphomas has known many changes over time. Nowadays, lymphomas comprise Hodgkin and non-Hodgkin lymphoma (HL, NHL respectively). It is a malignant neoplasm that originates from lymphoid organs and tissues, and derives from cells of the immune system (B, T or NK (natural killer) lymphocytes).
   - *Plasma cell neoplasm*: It is an abnormal plasma cell that develops from B lymphocytes in the bone marrow and soft tissues NIC 2020.

3.6.2 Complications of Cancer

1. **Metastasis**:
   The formation of metastasis in cancer is not completely clear and implicates different mechanisms. It can be the consequence of epithelial to mesenchymal transition (EMT) through many gene transformations. Or, it can find its origin in steam cells Thomas N. Seyfried1 and Huysentruyt 2013. Tumor spread implicates its capacity to move through the walls of conjunctive tissue, and then to lymph nodes and blood vessels, and this leads leads to a spread of cancer cells through the body.

2. **Tissue Remodeling**
   Tissue remodeling can be considered as an actor of metastasis formation. In physiological state, epithelial cells in conjunctive tissue are supressed, but tumor cells are capable of stopping apoptosis signals and modify physiological reaction so that it can spread out of its original organ Buache and Rio 2014.

3.6.3 Pathophysiology of DIC in Cancer

Malignancy is considered to be the third most common cause of DIC only after sepsis and trauma with close to 7% of cases related to an underlying malignancy. Malignancy in itself is a hypercoagulable condition, with advancing age, male gender, presence of primary tumor necrosis and advanced stage further increasing the risk of developing DIC in the malignant disorders Balwinder Singh 2014. Cancer-related DIC may present in one of these 3 forms:

- The procoagulant form
- The hyperfibrinolytic form.
- The subclinical form, where the amounts of thrombin and plasmin generated do not cause obvious clinical manifestations but can be reflected in laboratory markers of coagulation or fibrinolysis activationSohal et al. 2020.

1. **Solid Tumors**: Solid tumors have been shown to influence coagulation pathways by a number of different mechanisms:

    - Many solid tumors but also hematological malignant cells express tissue factor on the cell surfaces, which in conjunction with factor VII activates the extrinsic pathway of coagulation. Tissue factor strongly correlates with fibrin deposition in the tumor stroma, reflecting perivascular activation of coagulation.
    - A cysteine proteinase with factor X activating properties is found in certain malignant tumors (i.e. lung and breast carcinomas, kidney and colorectal adenocarcinoma) and contributes directly to activation of coagulation.
    - Other thrombogenic factors are related to enhanced adhesion and aggregation of platelets, or the secretion of mucin-like substances that may induce coagulation activation Kramer et al. 2002.

2. **Hematological Malignancies:** The hematological malignancies are most often complicated by DIC. Acute promyelocytic leukemia (APL), a variant of acute leukemia, is associated with DIC in the majority of patients, and this causation has been related to:

    - the release of various pro-coagulant enzymes present in the abnormally large granules present in leukemic promyelocytes.
    - a higher level of annexin II in APL cells which leads to increased production of plasmin. Hence, the unopposed fibrinolysis may also lead to bleeding Balwinder Singh 2014.
    - an acquired functional α2-antiplasmin and TAFI deficiency contributing to the pronounced hyperfibrinolysis, with high levels of fibrinogen and fibrin degradation products Kramer et al. 2002. A high incidence of DIC has also been described in adult patients with acute lymphoblastic leukemia (ALL) and in patients with de novo Philadelphia chromosome positive ALL. While at presentation DIC was only detected in 10% of these patients, it was found in 80% during induction therapy. At present the pathogenesis of DIC in these patients is not clear.

3.7 Diagnosis of DIC

Making the diagnosis of DIC starts with identifying an underlying associated disease state Table 5.11. Once this is established, the diagnosis entails a combination of laboratory values along with an analysis of the clinical presentation.

The difficulty with diagnosing DIC is that there is no gold standard and no pathognomonic test. There have been several scoring systems developed for DIC to assist in standardizing the diagnosis Do 2020.

History and physical examination
Platelet count
Examination of stained blood smear
Prothrombin time (PT)
Partial thromboplastin time (PTT)
Thrombin clotting time (TT)
Fribrinogen estimation

Table 3.2 Initial Laboratory Tests in the Diagnosis of DIC
Karpatkin 1971

Since there is no single laboratory test that can establish or rule out the diagnosis of DIC, a diagnosis of DIC should be made based on an appropriate clinical suspicion supported by relevant laboratory tests Gando et al. 2016.

Different levels of exploration are then recommended to establish the diagnosis: screening tests and confirmatory tests Dumas et al. 2012.

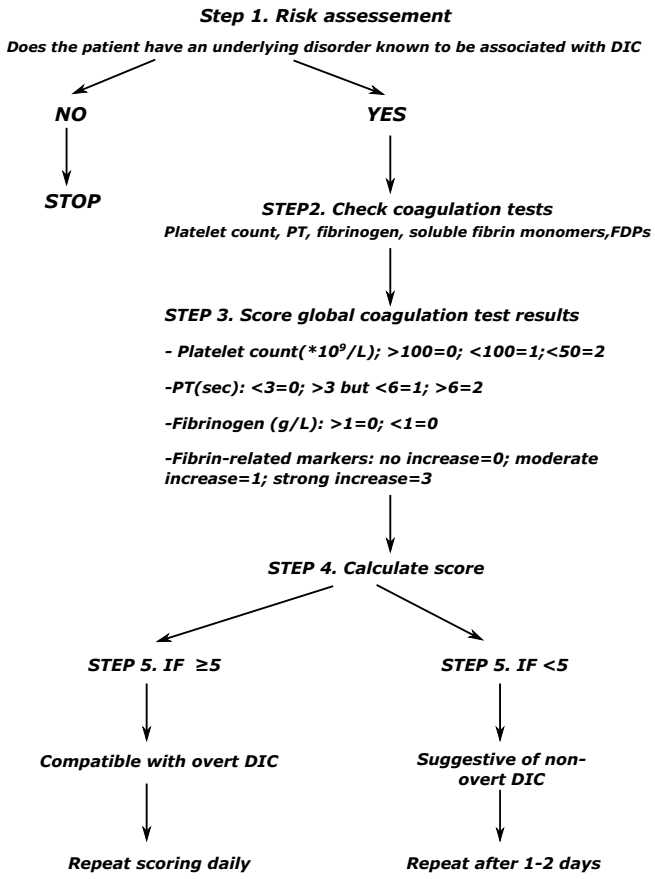

Figure 3.8: Five-step Algorithm for the Diagnosis of Disseminated Intravascular Coagulation (Lippi 2006)

Scores 3.6

3.7.1 Global Coagulation Tests in DIC

1. **Platelet Count**
   A reduction in the platelet count or a clear downward trend at subsequent measurements is a sensitive (though not specific) sign of DIC. Thrombocytopenia is a feature in up to 98% of DIC cases with the platelet count $<50 \times 10^9/l$ in approximately 50%. A low platelet count correlates strongly with markers of thrombin generation, because thrombin-induced platelet aggregation is mainly responsible for platelet consumption Levi et al. 2009.

   It should be remembered that a declining trend is not very specific for DIC because conditions associated with DIC such as acute leukemia and sepsis can also have thrombocytopenia in the absence of DIC Article 2014.

2. **Prothrombin Time and Activated Partial Thromboplastin Time (PT and APTT)**
   The PT or aPTT is prolonged in about 50–60% of cases of DIC at some point during the course of illness Levi et al. 2009. At the same time, at least in half the patients with DIC, PT and aPTT are found normal or shortened due to the presence of circulating activated clotting factors like thrombin or Xa. Thus, a normal PT or aPTT do not exclude DIC and repeated monitoring is required.

3. **Thrombin Cloting Time**
   The thrombin clotting time is usually prolonged. Thus, it measures only the

very last part of the 28 coagulation reaction-conversion of fibrinogen to fibrin. It is prolonged if fibrinogen is grossly depleted (usually below 80 mg100ml). The more usual cause for its prolongation in intravascular coagulation is the presence of fibrin degradation products Karpatkin 1971.

4. **Fibrinogen**
   Measurement of fibrinogen has been widely advocated as a useful tool for the diagnosis of DIC, but in fact it is not very helpful in most cases Levi et al. 2009. Hypofibrinogenaemia for diagnosis of DIC carries very low sensitivity and was associated only with severe forms of DIC.

   Fibrinogen level can be normal in nearly half of the patients, and hence, serial measurements are indicated.

3.7.2 Confirmatory Tests for the Diagnosis of DIC

1. **Fibrin Degradation Products**

   Fibrin degradation products is a measure of increased fibrinolytic activity which is increased in DIC. They may be detected by specific ELISA's or by latex agglutination assays. FDPs measurement is suitable for emergency cases, but its specificity is not sufficient to discriminate DIC from other pathologies Levi and Meijers 2011.

2. **D-dimer**
   New assays that can specifically detect neo-antigens on degraded cross-linked fibrin called the D-dimer have been developed. D-dimer levels are also found elevated in conditions like trauma, recent surgery or venous thromboembolism. Hence, it is not a specific test for DIC. It can also be raised in liver and renal impairment as a result of its impaired metabolism and excretion. However, it is of value when associated with a declining platelet count and prolonged PT and aPTT. Though much debate is underway regarding the cut-off level of D-dimer, clinician's experience, available circumstance and other supportive laboratory values are crucial to the diagnosis of DIC Dumas et al. 2012.

3. **Soluble Fibrin Monomer**
   Soluble fibrin monomer (SF) measurements offer theoretical advantages in DIC in reflecting thrombin action on fibrinogen. Because SF is only generated intravascularly, it should therefore not be influenced by extravascular fibrin formation when caused by local inflammation or trauma. Most clinical studies have shown a sensitivity of 90–100% for the diagnosis of DIC but a very low specificity. However, its incorporation into the ISTH DIC scoring system instead of D-dimer as the fibrin-related marker can improve the specificity of diagnosing DIC Dumas et al. 2012.

4. **Soluble Fibrin Monomer Complex**
   The search for soluble complexes consists in identifying indirectly the presence of fibrin monomers in a patient's plasma. Fibrin monomers are specific for intravascular coagulation activation, since their presence is a consequence of the action of thrombin on circulating fibrinogen. The search for soluble complexes is carried out by "paracoagulation" tests, ethanol test and protamine sulphate test. However, a positive result is a very strong argument for the diagnosis of DIC. They are falsely negative in the event of an intense drop in fibrinogen levels

Fibrin split products increased
Fibrinogen level decreased
Platelet count decreased
Partial thromboplastin time (PTT) prolonged
Prothrombin time (PT) prolonged
Thrombin time (TT) increased
Clotting factor analysis defines which factors have been consumed

Table 3.3 Laboratory Values for DIC

(fibrinogen $\leq 0.5 \mathrm{g\,L^{-1}}$); they become positive when fibrinogen is reactivated by therapy. In subacute and chronic DIC, the ethanol test is sometimes negative Dumas et al. 2012.

3.7.3 Other Markers of Haemostasis

1. **Factor VIII Assay**
   The level of factor VIII is frequently reduced in disseminated intravascular coagulation. Merskey and co-workers found it to be reduced in all patients with acute DIC and in many patients with the subacute syndrome. However, a normal level of this factor does not rule out the diagnosis, and in some instances, this assay has revealed very high levels, up to 300% or 400% of normal Karpatkin 1971.

2. **Factor V Assay**
   Merskey and co-workers found factor V to be reduced in acute defibrination and in many cases of subacute defibrination. It is rarely normal or slightly elevated Karpatkin 1971.

Besides the above-described tests, several other markers have been proposed as useful in diagnosing DIC. Most of these molecular markers, e.g., thrombin-antithrombin (TAT) complexes and prothrombin fragment1+2 (F1+2), are available only in specialized laboratories and even then they are not routinely performed and standardized to this setting Toh et al. 2016.

The natural anticoagulants antithrombin and protein C are often reduced in DIC and these have been shown to have prognostic significance. The availability of chromogenic assays rather than a reliance on ELISA techniques has meant that results can be made available more rapidly. Nonetheless, their general availability is still limited and single determinations are neither sensitive nor sufficiently specific for DIC. In very rare cases, purpura fulminans develops secondary to profound acquired deficiency of protein S. This is most commonly described following varicella infection. Although management strategies for this specific indication are not clear, the association is notable Article 2014.

3.7.4 Other Biological Abnormalities

In association with haemostasis disorders, other abnormalities can be described and correlated to the clinical context:

- Presence of schizocytes on the blood smear, with slight increased hemoglobinemia, and secondarily, free bilirubin.

- Elevation of creatinine, azotaemia in cortical necrosis.

- Cholestase syndrome (elevated alkaline phosphatases) and/or hepatic cytolysis (AST, ALT).

3.7.5 Scoring Systems

As impractical as it may seem, we ideally need a unique DIC score for each of the underlying diseases that cause DIC. The absence of an unquestionable diagnostic standard for DIC, will continue to fuel research and validation in search of an ideal diagnostic score with equally high sensitivity and specificity, clinical bedside easy applicability, ready availability, and suitability for a wide array of DIC causing diseases.

Scoring systems to diagnose DIC were developed by the Japanese Ministry of Health and Welfare (JMHW) in 1988 from its older 1983 criteria, ISTH/SSC in 2001, and by the Japanese Association for Acute Medicine (JAAM) in 2006.

All three consist of assays of global markers of coagulation and fibrinolysis that are commonly available in all hospitals Akhilesh Kumar Tiwari, MD1* , Michell Gulabani, MD2, Prashant Dass, MD3 and Rishi Raj Sanjay 2013.

1. **The JMHW Scoring System**

   The JMHW DIC diagnostic score is as depicted in Table 3.4. Used exclusively in hematological malignancies (HPT) it has shown moderate sensitivity and high specificity (HPT).

   Its reliance on subjective clinical symptoms of bleeding and thrombosis induced organ dysfunction for which a point each is given, compromises its sensitivity compared to the newer DIC diagnostic scoring systems.

   Differentiation is also made between patients with (HPT+) and without (HPT-) hematopoietic malignancies. Indeed, bleeding symptoms in HPT are given one point and changes in platelet count are not given a score in HPT+ patients. A score of four or more in HPT+ and seven or more in HPT- patients is considered diagnostic for DIC Akhilesh Kumar Tiwari, MD1* , Michell Gulabani, MD2, Prashant Dass, MD3 and Rishi Raj Sanjay 2013.

-	DIC criteria (score)
Underlying disease	-
Yes	1
Clinical symptoms Bleeding symptoms	-
Yes	1
No	0
Organ symptoms	-
Yes	1
No	0
Laboratory tests Platelets count ($\times 10^3$ μL^{-1})	-
$\leq$120	1
$\leq$80	2
$\leq$50	3
FDP ($\mu g\, dL^{-1}$)	-
$\geq$10	1
$\geq$20	2
$\geq$40	3
Fibrinogen (mg/dL))	-
$\leq$150	1
$\leq$100	2
PT ratio	-
$\geq$1.25	1
$\geq$1.67	2
Diagnosis of DIC	-
DIC	$\geq$7
DIC suspected	6

Table 3.4 The Diagnostic Criteria for DIC by the Japanese Ministry of Health and Welfare (JMHW) Sugawara et al. 2013

FDP, Fibrin, and Fibrinogen Degradation Products

2. **The JAAM Scoring System**
   In critically ill patients, the close association between coagulation and inflammation is evident by the role of systemic inflammatory response syndrome (SIRS) in development of DIC.

   Realizing that rapid diagnosis and prompt treatment would improve outcomes in DIC, JAAM proposed a new JAAM DIC score for the critically ill patients (Table 3.5) Akhilesh Kumar Tiwari, MD1* , Michell Gulabani, MD2, Prashant Dass, MD3 and Rishi Raj Sanjay 2013.

The diagnostic algorithm	-	Score
SIRS criteria	≥3	1
Platelet counts ($109\,L^{-1}$)	≥120 ≥80-<120 or more than 30% decreased within 24h	0 1
-	≤80 or more than 50% decreased within 24h	3
Prothrombin time (value of patient/normal value)	<1.2 ≥1.2	0 1
Fibrin/fibrinogen degradation products ($mg\,L^{-1}$)	≥10,<25 ≥25	0 3
Diagnosis	0-2 4 points or more	0 DIC

Table 3.5 Japanese Association for Acute Medicine Scoring System (Takemitsu et al. 2010)

Increased sensitivity of this score for diagnosis of DIC has been shown in critically ill patients, trauma, and obstetric disorders Akhilesh Kumar Tiwari, MD1* , Michell Gulabani, MD2, Prashant Dass, MD3 and Rishi Raj Sanjay 2013.

3. **The ISTH Scoring Systems** Prior risk assessment for identification of an underlying clinical condition that may be associated with DIC is mandatory before using the overt DIC score. Also, multiple FRMs (FDP, D-dimer & SF) are used as against FDP alone in JMWH and JAAM DIC scores.

   A score in excess of five is compatible with diagnosis of overt DIC. A score less than five is suggestive (not affirmative) for non-overt DIC and needs to be repeated in the next one to two days Akhilesh Kumar Tiwari, MD1* , Michell Gulabani, MD2, Prashant Dass, MD3 and Rishi Raj Sanjay 2013.

The ISTH Overt Scoring System The ISTH Sub-Committee of the Scientific and Standardization Committee (SSC) on DIC has recommended the use of a scoring system for overt-DIC based on the Japanese Ministry of Health and Welfare score, which has demonstrated a close correlation between an increasing score and increasing mortality.

The ISTH criteria proposed a 5-step diagnostic algorithm to calculate a DIC score, utilising simple laboratory tests that are available in almost all hospital laboratories Levi et al. 2009.

The levels of fibrin related products are given the highest weight among the laboratory tests, and two points are assigned for reductions in the platelet count, which lower the specificity of DIC diagnoses in patients with leukemia.

Though objective abnormal laboratory values are used for its diagnosis, no objective clear cutoff values have been defined for FDP and SF. However, for D-dimer a level $>4.0\,\mu g\,mL^{-1}$ is considered a moderate increase, and $>40\,\mu g\,mL^{-1}$ is a strong increase Akhilesh Kumar Tiwari, MD1* , Michell Gulabani, MD2, Prashant Dass, MD3 and Rishi Raj Sanjay 2013.

1. Risk assessment: Does the patient have an underlying disorder known to be associated with DIC? if yes: Proceed if no: Do not use this algorythm 2. Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related markers). 3. Score global coagulation tests results: - Platelet count (>100=0, <100=1, <50=2) - Elevated fibrin related markers (eg D-dimer, fibrin degradation products) (no increase= 0, moderate increase= 2, strong increase= 3) - Prolonged prothrombin time (<3s= 0, >3s but <6= 1, >6= 2) -Fibrinogen level (>1 g L^{-1}= 0, <1 g/L = 1 4. Calculate score if ≥5: compatible with overt DIC: repeat daily if <5: suggestive (not affirmative) of non-overt DIC: repeat next 1-2 days.

Table 3.6 Scoring System for Overt Disseminated Intravascular Coagulation (Hayakawa et al. 2007)

The ISTH Non-Overt Scoring System Using kinetic components and sensitive molecular markers, such as soluble fibrin and TAT, the ISTH proposed a scoring system for "nonovert DIC" that may detect the presence of hemostatic dysfunction when it is not yet at the stage of frank decompensation, namely overt DIC (table 3.9) Gando 2012.

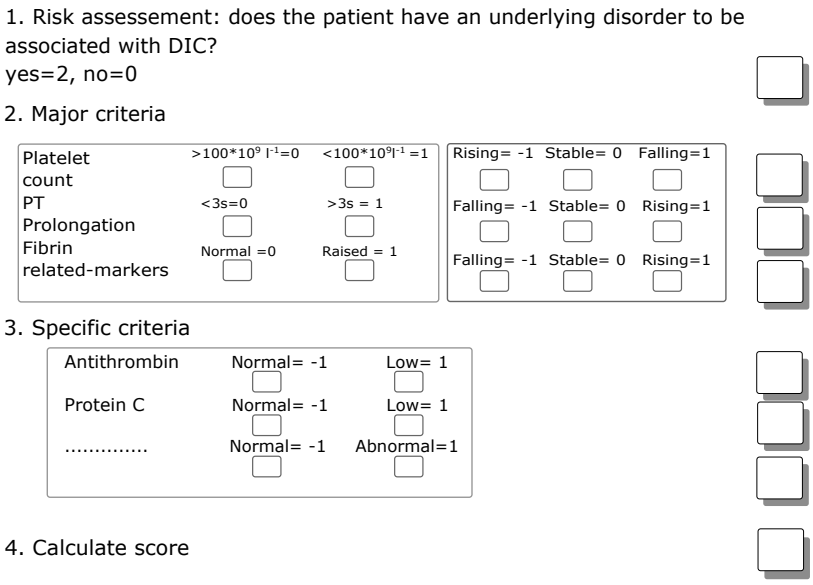

Figure 3.9: Scoring System for Non-overt Disseminated Intravascular Coagulation (Takemitsu et al. 2010)

In the presence of an underlying disease known to be associated with DIC, major and specific criteria are to be considered in this scoring system. Similar global coagulation tests are used as in overt-DIC, but with emphasis on trends over time, in order to increase the sensitivity. The SSC recommends daily measurements. Specific criteria require AT or protein C or TAT complexes depending on local conditions.

3.7.6 Differential Diagnosis of DIC, Coagulation Defect due to Liver Failure and Primary Pathological Fibrinolysis

Hepatocellular damage, whether due to infection, drugs, or chemicals, can cause a marked coagulation defect. Most clotting factors and plasminogen are synthesized exclusively in the liver, and levels of all except factor VIII may decrease in liver disease. In addition, intravascular coagulation or low-grade fibrinolysis is sometimes associated with liver disease, and differential diagnosis is very difficult. An increased level of fibrin degradation products is good evidence that intravascular coagulation is at least partly responsible for the defect, and a low level of factor VIII is against the diagnosis of uncomplicated hepatocellular damage. Laboratory findings in the two diseases are summarized in Table 3.7 Karpatkin 1971.

-	DIC	Liver Disease	Primary Fibrinolysis
Platelet count	Reduced	Normal or Reduced*	Normal
Prthrombin time	Prolonged	Prolonged	Prolonged
Partial thromboplastin time	Prolonged	Prolonged	Prolonged
Thrombin time	Prolonged	Prolonged	Prolonged
Fibrinogen	Reduced	Reduced	Reduced
Factor VIII	Reduced or elevated	Normal or elevated	Reduced
Factor V	Reduced	Reduced	Reduced
F.D.P	Increased	Normal	Increased
Plasminogen	Decreased	Decreased	Decreased
Euglobulin lysis time	Normal	Short or normal	Markedly shortened

*Reduced when hypersplenism is associated with liver disease.

Table 3.7 Laboratory Differential Diagnosis between Disseminated Intravascular Coagulation (DIC), Liver Disease not Accompanied by DIC, and Primary Fibrinolysis Karpatkin 1971

Primary pathological fibrinolysis is the term used to describe a condition in which there is a sudden massive activation of plasminogen throughout the body, resulting in free circulating plasmin. This plasmin lyses fibrinogen and other clotting factors, resulting in decreased coagulation and haemorrhage. Fibrinogen degradation products which are formed are identical immunologically to fibrin degradation products and are therefore indistinguishable by most methods of measurement.

Until 10 years ago, this condition was diagnosed quite frequently, mainly in association with complications of labour. It now appears that the majority of those cases were in fact disseminated intravascular coagulation, and that primary pathological fibrinolysis is an extremely rare syndrome. Rskey and co-workers in 1967 had seen only five cases in the preceding 10 years, and none in the preceding 4 years. Laboratory findings in this condition are summarized in Table3.7 Karpatkin 1971.

3.8 Treatment of DIC

The therapeutic cornerstone of DIC is the treatment of the underlying disorder. In fact, if the malignant disease can be brought into remission, the DIC will usually disappear simultaneously Levi 2007a.

It is also clear that a good understanding of the pathophysiology and natural history of the underlying disease and trigger mechanisms involved contribute a great deal to the logical and rational management of these patients Feinstein 1988.

However, patients with DIC resulting from sepsis, hematologic malignancy, or obstetric disease can be successfully treated for DIC, whereas DIC associated with solid cancers may not respond to standard treatments Sohal et al. 2020.

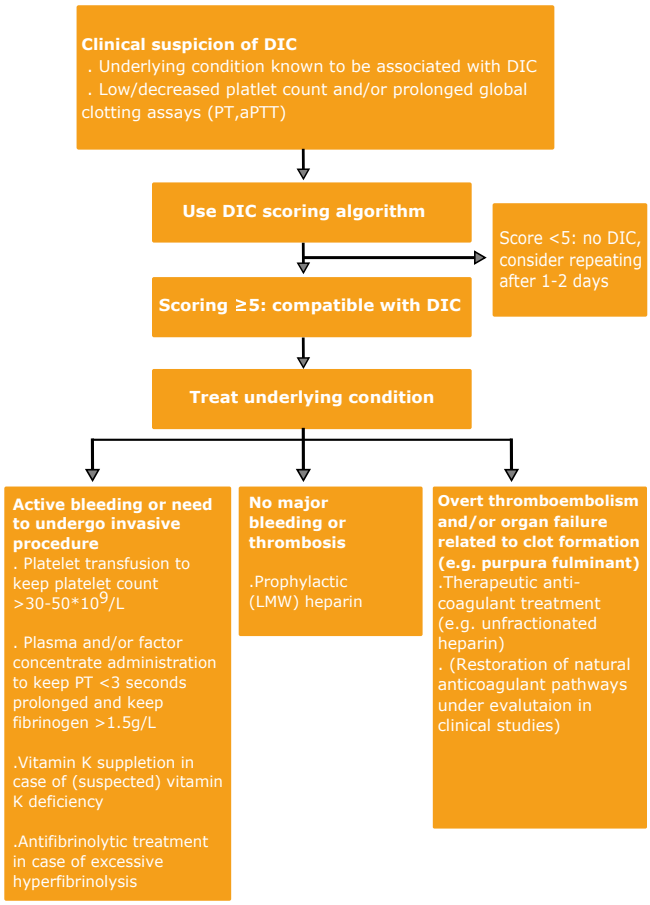

Figure 3.10: Flowchart for the Diagnostic and Therapeutic Management of DIC Facts 2020

3.8.1 Replacement of Blood Products

1. **Plasma and Platelet Transfusion**
   Thrombocytopenia and clotting factor deficiency may predispose for major haemorrhagic complications. Nevertheless, transfusion of plasma or platelets should not be prescribed based on laboratory tests only Levi 2014, but is only indicated in patients with active bleeding and in those requiring an invasive procedure or who are otherwise at risk for bleeding complications.

   The presumed efficacy of treatment with plasma or platelets is not based on randomized controlled trials, but appears to be rational therapy in bleeding patients or in patients at risk for bleeding with a significant depletion of these elements Levi et al. 2004. In general, platelets are administered to patients with a count of less than 50-109 L^{-1}, who are actively bleeding. A much lower threshold (<30-109 L^{-1}) may be used if there is no active bleeding Thachil and Toh 2009.

1. Fresh Frozen Plasma (ffP):
   In the presence of active bleeding and prolonged PT and aPTT, administration of fresh frozen plasma (FFP) (10–20 $mL\,kg^{-1}$) can be useful Thachil and Toh 2009.

2. Prothrombin Complex Concetrate (PCC):
   If FFP transfusion is not possible due to fluid overload, PCC (25–30 Ukg^{-1})) may be tried. These concentrates will only partially correct the defect because they only contain vitamin-K-dependent coagulation factors Thachil and Toh 2009.

3. Fibrinogen:
   A level of 1 $g\,L^{-1}$ is considered to be haemostatically adequate although a higher threshold for replacement would be advisable in patients with DIC as fibrinogen can be consumed rapidly. Fibrinogen is usually given as cryoprecipitate, and it should be reserved for severe hypofibrino-genemia (<50 $mg\,dL^{-1}$ or for active bleeding with a fibrinogen level less than 100 $mg\,dL^{-1}$ Maxson 2000.

3.8.2 Anticoagulants

1. **Heparin/Heparinoid**
   Heparin/Heparinoid includes UFH, LMWH, and danaparoid sodium (DS). Though heparin or heparinoid does not itself have any anticoagulant activity, it increases the activity of AT to suppress thrombin activity, and thus improves the hemostatic abnormalities of DIC. The side effects include haemorrhage and heparin induced thrombocytopenia (HIT) Wada et al. 2010.

   Administration of heparin in DIC remains controversial. Because of the difficulty in conducting well-controlled clinical trials, the efficacy of heparin in the treatment of DIC has not been documented Maxson 2000.

	Object	Drug	Mortality (%)	Period (days)
Phase III trial of APC from plasma products	DIC	APC	20.4	28
		UFH	40.0	
Phase III trial of Danaparoid sodium	DIC	Danaparoid sodium	16.9	6
		UFH	12.1	
Phase III trial of Dalteparin sodium	DIC	Dalteparin sodium	6.6	6
		UFH	12.1	
Retrospective study	DIC	FOY	25	14
KyberSept study	Severe sepsis	ATIII	38.9	28
		None	38.7	
Prowess trial	Severe sepsis	APC	24.7	28
		None	30.8	
OPTIMIST study	Severe sepsis	TFPI	34.2	28
		None	33.9	

UFH: unfractionated Heparin.

Table 3.8 Clinical Trials for DIC or Severe Sepsis Wada 2004

2. **Hirudin**
   Hirudin is a potent and specific direct thrombin inhibitor. In contrast to heparin, its activity is not dependent on antithrombin III. Therefore, recombinant hirudin is capable of inhibiting clot-bound thrombin. Hirudin appeared to be effective in treating DIC in animal studies, and in one series of 5 patients with hematological malignancy and DIC. The high risk of bleeding with hirudin treatment, as for example shown in initial clinical trials may potentially limit the use of hirudin in these patients Jonge 2020.

3.8.3 Coagulation Inhibitors

1. **Antithrombin**

   Blood level of AT is markedly reduced in patients with diseases such as sepsis. Based on successful pre-clinical results, the use of antithrombin III concentrates in patients with DIC has been studied relatively intensively.

   All trials show some beneficial effects in terms of improvement of laboratory parameters, shortening of the duration of DIC, or even improvement in organ function Levi et al. 2004.

2. **Protein C System**
   Based on the notion that depression of the protein C system may significantly contribute to the pathophysiology of DIC, the supplementation of activated protein C might potentially be of benefit Levi et al. 2004.

3. **Thrombomodulin**
   A new therapeutic agent that is currently under evaluation is human soluble thrombomodulin that is produced through recombinant techniques Levi 2014. TM binds thrombin and the thrombin-TM complex activates PC to APC. TM also binds high-mobility group-B1 (HMGB-1), thus inhibiting the inflammatory process. In RCT for rTM in sepsis and hematopoietic malignancy rTM significantly improved DIC and its bleeding symptoms in comparison to UFH. As a result, TM appears to be an effective drug for the treatment of DIC Wada et al. 2010.

4. **TFPI**
   There are two possibilities for specific inhibition of the tissue factor pathway: recombinant TFPI (a naturally occurring, genetically engineered FT-factor VIIa inhibitor) and FFR-VIIa (a covalent inhibitor Phe-Phe-Arg chloromethylketone, an inactive substitute for FVIIa also produced by genetic engineering). Inhibitors of the tissue factor pathway have not been tested in the treatment of DIC, but they do not represent a promising pathway Eurotext et al. 2020.

3.8.4 Fibrinolytic Inhibitors

DIC should not be treated with antifibrinolytic agents that may in fact cause deterioration of microvascular thrombosis. In some cases, DIC and pathological systemic hyperfibrinolysis (or hyperfibrinogenolysis) may coexist. This is known as DIC with the hyperfibrinolytic phenotype (i.e acute promyelocytic leukaemia (APL) and prostatic carcinoma). In these cases, antifibrinolytic treatment may be applicable Gando et al. 2016.

1. **Epsilon Aminocaproic Acid (EACA)**

   EACA an antifibrinolytic agent, can be given (combined with heparin) to inhibit the activity of circulating plasmin during uncontrolled life-threatening bleeding. EACA must never be administered unless the patient is receiving concurrent heparin therapy. Cardiac status, electrolytes, and renal output must be monitored closely Maxson 2000.

Drug	Trial	Design	Subject	Result	Ref
Antithrombin	KiperSept	Double-blind, placebo controlled, multicentre	Severe sepsis	Failed	140
	KyberSept	Retrospective sub-group analysis of the KyberSept trial	DIC in severe sepsis	Significant mortality reduction (P=0.024)	17
	JAAMDICAT	Prospective multicentre	Dic in sepsis and severe sepsis	Significant improvement of DIC (P=0.015) and doubling recovery rate without risk of bleeding	147
Tissue factore pathway	OPTIMIST	Double-blind, placebo controlled, multicentre	severe sepsis	Failed	141
. Recombinant activated protein C	PROWESS-SHOCK	Double-blind, placebo controlled, multicentre	Sceptic shock	Failed	142
	Prowess	Retrospective sub-group analysis of the PROWESS trial	DIC in severe sepsis	A trend towards greater risk reduction in mortality	16
Plasma-derived activated protein C	NA	Randomized, prospective, double blind, multicentre	DIC in various underlying diseases	Significant mortality reduction withou increasing bleeding (P=<0.05)	143
. Recombinant soluble thrombomodulin	NA	Randomized, prospective, double blind, multicentre	DIC in hematological malignancy or infection	Significant improvement of DIC without risk of bleeding (P value is not provided, but the resolution rate of 95% CI was described)	151
	NA	Double-blind, placebo controlled, multicentre	Suspected DIC in sepsis	Evidence suggestive of efficacy supporting further developement of this drug in sepsis-associated DIC	157
	NA	Double-blind, placebo controlled, multicentre	Severe sepsis and coagulopathy	ongoing	177

DIC: disseminated intravascular coagulation, NA: not available.

Table 3.9 Studies on Anticoagulant Factor Concentrates Gando et al. 2016

2. **Tranexamin Acid**
   Tranexamic acid is a newer and more potent antifibrinolytic agent with fewer undesirable side effects. It is used typically to treat DIC caused by acute promyelocytic leukemia Maxson 2000.

3.8.5 Recombinant Activated Factor VII (Novoseven®)

This treatment could be considered as a life-saving and powerful prothrombotic agent for life-threatening bleeding Eurotext et al. 2020n.

1.Patients with DIC, without bleeding or thrombosis(i.e.non-overt non symptomatic type),with a treatable underlying disorder	
Recommendation	In a patient with overt DIC, without bleeding or thrombosis, and with a treatable underlying disorder, there was a consensus that physicians should provide individualised strategy according to the underlying condition triggering the coagulopathy. In DIC patients with acute promyelocytic leukemia, we suggest prophylactic platelet transfusion to maintain a platelet level at leaqt $>20 \times 10^9 L^{-1}$; in severe sepsis, we suggest a phrophylactic dose of LMWH and prophylactiv platelet transfusion to maintain a platelet level at least above $>20 \times 10^9 L^{-1}$; in DIC secondary to pregnancy complications, we suggest a prophylactic dose of LMWH, in particular during the post-partum period, and prophylactiv platelet transfusion to maintain a platelet level at least above $>20 \times 10^9 L^{-1}$.
2.Patients with over DIC, minor bleeding, and an untreatable underlying disorder	
Recommendation	Haemostatic tranfusion support with blood products should be given for a limited period of time to a patient with DIC, minor bleeding and an untreatable underlying disorder. In particular, we suggest to continue with platelet transfusion until the bleeding cease and to maintain a platelet level at least above $>20 \times 10^9 L^{-1}$.
3.Platelet count in patients	
Recommendation	A platelet count $>50\times 10^9 L^{-1}$ is suggested in all DIC patients with an active major bleeding. In non-bleeding patients, the trigger for platelet transfusion is between 20 and $30\times 10^9 L^{-1}$
4.Duration of VTE prophylaxis in patiens with over DIC	
Recommendation	Pharmacological VTE prophylaxis should be stopped in case of bleeding or when platelet counts is less than $30\times 10^9 L^{-1}$ and/or PT ratio is more than 1.5 and/or PTT ratio is more than 1.5 and/or fibrinogen level $<1\,g\,L^{-1}$
5.Acute DVT and/or PE in patients with overt DIC and concomittant bleeding	
Recommendation	We suggest to use a retrievable IVC filter in DIC patients with acte VTE and concomittant bleeding. When bleeding is ceased, risk and benefits of starting anticoagulation should be assessed daily through the close monitoring of patient's status, laboratory tests and treatement of the underlying condition.

Table 3.10 Final Recommendation for the Treatment of DIC Squizzato and Wada 2015

3.9 Management of DIC in Cancer Patients

Only the etiological treatment seems to be effective for the control of DIC secondary to a solid tumor. Substitute therapies only allow to await the effectiveness of

the etiological treatment. No specific treatment for haemostasis has been validated and they have unlikely to be validated by controlled studies in view of the heterogeneity of the situations responsible for DIC and their low incidence Eurotext et al. 2020.

In haematological malignancy, chemotherapy may often exacerbate coagulation abnormalities and bleeding in APL and other hematologic malignancies. Therefore, the role of supportive treatment that aimed to improve coagulation abnormalities is of undoubted importance in this phase of the disease, in particular when bleeding complications occur. The utility of other old or newer hemostatically active agents remains uncertain (table3.11) Franchini et al. 2010.

Intervention	Subclinical DIC	Overt DIC
Therapy of the underlying disorder	in all cases, early, intensive and specific treatment. In APL, institution of ATRA at clinical suspition, even before molecular confirmation, in particular in the presence of high leukocyte count.	
Platelet transfusion	According to clinical need (chemotherapy)	Maintain platelet count $> 20\times10^{9}L^{-1}$; $>50\times10^{9}L^{-1}$ if bleeding occurs and in ALP.
Plasma (or derivative) transfusion	no	Maintain fibrinogen level $> 100\,mg\,dL^{-1}$ in bleeding APL patients.
Antithrombotic prophylaxis (LMWH, fondaparinux)	Consider in particular in patients with additional thrombosis risk factors and according to bleeding risk	Consider after starting chemotherapy (and ATRA in APL) when bleeding has been settled.
Antifibrinolytic agents	According to bleeding risk	Consider in life-threatening bleeding in APL?
rFVIIa	.	Consider in life-threatening bleeding?

APL: acute promyelocytic leukemia, ATRA: all-trans retinoic acid, LMWH: low molecular weight heparin.

Table 3.11 Approaches for Management of Patients with Disseminated Intravascular Coagulation and Hematologic Franchini et al. 2010

Chapter 4

Material and Methods

4.1 Material and Methods 1: Review of the literature

The first objective of this work is to hilight the frequency of the occurence of DIC in patients with Solid cancer and hematological malignancies.

It also aims to:

- Explore laboratory findings, compliactions and risk factors in patients with and without DIC.
- Compare diagnostic and prognostic relevance between global coagulation tests and scores, and between different scoring systems.
- Explore the use of available and modified scores in predincting death in non-overt DIC patients.

Searches were conducted on the following databases:

- Pubmed
- Reasergate
- Google scholar
- Science direct
- SAGE journal

Search terms used were:

- Disseminated intravascular coagulation and malignancies or dic and malignancies.
- Disseminated intravascular coagulation and solid cancer or dic and solid cancer.
- Disseminated intravascular coagulation and hematological malignancy or dic and hematological malignancy.
- Disseminated intravascular coagulation in acute leukemia or dic in acute leukemia.
- Disseminated intravascular coagulation scoring system or different scoring system of dic in malignancy or diagnostic of overt /non overt disseminated intravascular coagulation (dic) according to different scoring system.

In order to be as exhaustive as possible, these terms were searched in all fields. The titles of the articles were read in order to make a first selection. Duplicates were then eliminated. The summaries of the articles were then searched in order to make a second selection. The articles that were retained were read in full and retained or not in the study according to the inclusion criteria. Some of the authors of the selected studies were contacted for further information.

Study Selection:

Exclusion Criteria:

Studies with the following characteristics were excluded for the review:

- Population studied other than cancer patients with and without DIC, (except for the part "The Relevance of using Scores in the Diagnosis of DIC").
- Abstracts that do not provide enough information for the assessment of the methodological quality.

Inclusion Criteria:

The criteria of the selection procedure were based on:

- Article that include population with cancer with and without DIC for groupe 1 and 2, and population with and without DIC with any underlying pathology for the part "The Relevance of using Scores in the Diagnosis of DIC".
- Articles that provide enough information for the assessment of the methodological quality.

There was no language restriction.

Data Processing:

This section is divided into 3 parts:

1. **Diagnosis of DIC with biological tests:** We studied two groups to see the effect of DIC on them using the prevalence of DIC and comparing patients who had DIC and those who did not through laboratory tests, risk factors and complications. The two groups were:
   1. Solid cancer: Which is characterized by abnormal cellular growths in "solid" organs such as breast or prostate.
   2. Hematological malignancy: It comprises a collection of heterogeneous conditions, all originating from cells of the bone marrow and the lymphatic system. There are three major groups: leukemia, lymphoma, and plasma cell neoplasms.
2. **The relevance of using scores for the diagnosis of DIC:** In this part ,we compared between global coagulation tests and scores.
3. **Comparison between different scoring systems** using the diagnosis rate and morbidity rate to see which is the most reliable by reporting their sensitivity and specificity for diagnosing overt and non-overt DIC.

4.2 Material and Methods 2: Practical Section

4.2.1 Material

1. **Patients**
   This is a case series study spread over a period of 9 months, from February 2020 to March 2020; then a break from April 2020 to August 2020 because of the world health crisis, and a resumption from September 2020 to November 2020. The study involved patients diagnosed with solid cancer in the oncology department of Blida Anti-Cancer Center.
   Inclusion Criteria
   Our study involved patients with recent solid cancer with and without metastasis.
   Exclusion Criteria
   All patients without solid cancer were excluded from our study, as well as those with advanced cancer, and those who refused to participate.

2. **Auomatons**

   Sysmex XP-300: It is an automatic blood counting machine that uses an impedancemetry technique. We used it for making blood count formula of selected patients.
   The coagulation automaton (DIAGON®): It is an automaton which determines coagulation measurements via chronometric techniques (prothrombin time, activated partial thromboplastin time, fibrinogenemia) or colorimetric techniques (antithrombin). We used it for coagulation exploration (PT, aPTT, fibrinogenemia and AT).
   Calibrated tubes: They were used for the measurement of erythrocyte sedimentation rate of the samples.
   Centifuge Rotofix 32A HETTICH: Samples were taken on 0.109M (3.2%) sodium citrate (Vacutainer R) and centrifugated at 2500g for 15 min.

4.2.2 Methods

a. Data Collection

The data of this series of cases were collected for each patient by using their medical record. For each patient, a data collection form was filled out (A.1 A.2). The clinical data collected from the records are: age, sex, personal and family history, type of cancer, complications, antimitotic treatment and former medical tests.

b. Blood Sampling

Blood was collected by vein; mainly at the elbow bend, on specific tubes for the required parameters (EDTA and Citrate tube). Pre-analytical phase (sample transportation and conservation) was respected.

c.Sample processing

The blood assessment of the 12 patients was performed in the central laboratory of Frantz Fanon University Hospital Center. The laboratory assessment included:

Erythrocyte sedimentation rate which represents the rate at which red blood cells in anticoagulated whole blood (EDTA tube) descend in a standardized tube over a period of one hour. It is a non-specific measure of inflammation. Normal values range between 4mm and 8mm for women, and between 3mm and 6mm for men.

Blood count formula which was carried out from a whole blood sample on EDTA (Vacutainer®). We were interested in the platelet count, white blood cell, hematocrite and the haemoglobin level (to explore any associated anemia or infection). Normal values range between 150 and 400 $g\,L^{-1}$) for PLT, 4 and 10 $\times$ $10^6 L^{-1}$ for WBC and between 37%- 46% for women and 40%-52% for men.

Determination of coagulation parameters:
The explored parameters were:

1. Routine parameters

Prothrombin time was determined by a chronometric method with magnetic reading using Neoplastin (BIO-PT) as an activator according to the manufacturer's recommendations. PT explores factor VII, extrinsic pathway factor, and common pathway factors X, V, II and fibrinogen. Normal values range between 11 and 13 seconds.

Activated partial thromboplastin time was determined by a chronometric technique with magnetic reading using the reagent BIO-CK as an activator according to the manufacturer's recommendations. The APTT explores contact factors (factors XII, XI) and factors IX, VIII, X, V, II and fibrinogen. The normal time depends on the activators and the cephalic used by each laboratory, and ranges from 30 to 40 seconds.

Fibrinogenemia was determined by the Von Clauss method of chronometry using the reagent BIO-FIBRI; its rate is normally included between 2 and 4$g\,L^{-1}$.

Prothrombin time, *activated partial thromboplastin time* and *fibrinogenemia* were determined on the coagulation automaton DIAGON®.

2. Specific parameters

The dosage of FDP was carried out using a semi-quantitative latex particle agglutination technique (FDP® Plasma). We considered a level of <10 as negative according to Wada et al. 2012 scoring system (a level of <10 was given 0 point).

Antithrombin level: It was determined on the automatic coagulation machine DIAGON® using a turbidimetric method with the reagent LIATEST®ATIII, its rate is normally from 80% to 120%.

c. Data Analysis and Data Entry:

We calculated score values for each patient based on their laboratory findings using the modified non-overt DIC score proposed by Wada et al. 2012. Then we examined the relation and correlation between the laboratory findings and the score values, and between laboratory findings and the presence or absence of non-overt DIC. Data processing was carried out on the IBM SPSS Statistics Viewer 25.

This section is divided into 2 parts:

- The first part is a summary of the mean findings in the selected patients.
- The second part represents a correlation between different risk factors and the occurrence of non-overt DIC in the selected patients.

For the calculation of score values, Wada et al. 2012 template provides 1 point when a 5-fold increase was observed in FDP's levels. We considered that the evolution of FDP's levels from <10 to >25 was enough to add 1 point to the existing score;

this is due to the used technique which was semi-quantitative, and to a lack of reagent that made the titration more difficult.

Statistical Analysis

- Qualitative variables were expressed as percentages and numbers, and quantitative variables were expressed as averages and mean ±SD (standard deviation) with a confidence interval of 95%.
- The relation between score values and score parameters was examined for statistical significance using student test (T).
- The relation between the age and score values for statistical significance was examined using Kruskal-Wallis test.
- The relation between FDP's levels and scores, and between risk factors, complications and score was determined using the chi square test.
- The correlation between score values and laboratory findings was examined using Pearson's correlation coefficient.
- The correlation between score values and FDP's levels was examined using Spearman's correlation coefficient.

A p-value<0.05 was considered to be statistically significant.

Chapter 5

Results

Setting: The documentary research carried out made it possible to identify a total of 150 articles:

- 110 Articles in the pubmed database
- 10 Articles in the research gate database
- 16 Articles in the google scholar database
- 2 Articles in the science direct database
- 4 Articles in the isth.org database
- 8 Articles from SAGE journal

A first selection was made by reading the titles and abstracts. It allowed to exclude 128 articles. The remaining 22 items were reviewed to eliminate duplicates.

We therefore included 22 studies in this review.

5.1 Group 1: Solid Cancer

5.1.1 Patients' Characteristics

Table 5.1 Epidemiologic Data of Solid Cancer Population in Selected Studies

charcteistics / study	No (cancer patients)	Age	Sex ratio (F:M)	Study Design
S.Sallah et al 2001	1117	26-88	500:617	Cohort study
Asakura et al 2001	6	-	-	Cohort study
Mei et al 2019	76	58(48-63)	33:43	Cohort study
Wada et al 1999	86	-	-	Cohort study
Kushimoto et al 2012	132	M 64(54-72)	43:89	Cohort study
Okamoto et al 2010	142	M 63(52-72)	47:95	Cohort study
Pasquini et al 1995	7	42-73	6:1	Case reports

M;median, F; female, M; male

Sallah et al. 2001 and Pasquini et al. 1995 included a population with solid cancer. The other studies included population with underlying diseases known to be associated with DIC. In Pasquini et al. 1995 and Asakura et al. 2001 studies, all patients already had DIC. There is a male predominance in the different studies' population, and the patients' age ranges from 42 to 89 years.

5.1.2 Tumor Sites Studied in the Solid Cancer Population:

Table 5.2 Distribution of Solid Cancer Population According to Tumor Sites

Type of cancer	S.Sallah et al 2001	Wada et al 1999	Pasquini et al 1995	Kushimoto et al 2012	Aota et al 2016
Lung	153	18	-	14	27
Breast	149	-	3	6	5
Colorectal	104	-	-	8	-
Head and neck	100	-	-	-	-
Brain	29	-	-	-	-
Ovary	42	-	-	3	-
Testicle	28	-	-	-	-
Pancreas	44	9	-	3	6
Kidneys	35	-	-	-	-
Stomach	43	29	4	28	32
Bladder	30	-	-	2	-
Liver	29	5	-	33	9
Bile duct	-	-	-	9	6
Prostate	140	6	-	7	5
Oral	-	-	-	4	-
Esophagus	-	-	-	3	-
Orthopedic	-	-	-	8	-
Total	1117	86	7	132	90

Studies in selected articles explored a large range of solid cancer types.

5.1.3 Diagnostic Criteria for DIC

Table 5.3 DIC Diagnostic Criteria in Selected Studies

Characteristics / Study	Global Coagulation Tests				Hemostatic Markers						Other
	PT	aPTT	Fg ($mg\,dL^{-1}$)	PLT (10^9)L^{-1}	D-dimer ($\mu g\,mL^{-1}$)	FDPs ($\mu g\,mL^{-1}$)	sFM ($\mu g\,mL^{-1}$)	TAT ($ng\,mL^{-1}$)	PPIC ($\mu g\,mL^{-1}$)	AT (%)	PBS
S.Sallah et al 2001*	↑	↑	<200	<150	>0.5	↑				<80	+
Wada 1999	ratio >1.24		<150	<80	>2	>10	>100	>15	>1.5		
Pasquini et al 1995	PA:<70%		<150	<140		>32	+			<84%	
Kushimoto et al 2012	ISTH overt-DIC diagnostic criteria3.6										
Mei et al 2019	ISTH overt-DIC diagnostic criteria 3.6										
Okamoto et al 2010	Modified JMHLW diagnostic criteriaA.1										
Asakura et al 2001	JMHW diagnostic criteria 3.4										
Kawasugi et al 2011	ISTH and JMHW diagnostic criteria										

PT; prothrombin time, aPTT; activated thromboplastin time, Fg; fibrinogen, PLT, platelet count, FDPs, fibrin degradation products, sFM; soluble fibrin monomers, TAT; thrombin-antithrombin, PPIC; plamin-planinogen inhibitor, AT; antithrombin, PBS; periferal blood smear, PA; prothrombin activity

* The presence of at least 3 of the mentioned coagulation abnormalities in a patient with thrombosis or hemorrhage

Different Criteria were used depending on the country, population and the purpose of the study.

5.1.4 Laboratory Findings in DIC Patients

Table 5.4 Global Coagulation Tests Results in Solid Cancer Patients with DIC

	S.Sallah et al 2001	Wada 1999	Asakura et al 2001	Pasquini et al 1995	Kawasugi et al 2011
PT	↑	ratio >1.24	12.9 s (12.0–13.9)	PA 19-54%	INR M 1.43 (1.25 – 1.80)
aPTT	↑	-	-	37-100	-
PLT(10^9L^{-1})	M 52.5	<80	70(28–99)	23-102	M 42 (25 – 77)
Fibrinogen(mg dL^{-1})	M 129	<150	213(110–352)	47-144	182 (115 – 277)
WBC(10^3µL^{-1})	-	-	10.5(6.8–17.8)	-	-

WBC; white blood cells, PT; prothrombin time, aPTT; activated thromboplastin time, PLT platelet count, M: median, INR; international normalized ratio, PA: prothrombin activity

All studies reported abnormal global coagulation findings in solid cancer patients with DIC.

Table 5.5 Hemostatic Markers in Patients with DIC

	S.Sallah et al 2001	Mei et al 2019	Asakura et al 2001	Wada 1999	Pasquini et al 1995	kushimoto et al 2012	Kawasugi et al 2011
D-dimer($\mu g\,mL^{-1}$)	↑	-	-	>2	-	-	21.8 (11.8 – 34.7)
FDPs ($\mu g\,mL^{-1}$)	↑	-	69.8 (40.3–122.4)	≥10	-	>10	40.4 (27.0 - 72.1)
AT(%)	M 68(23-113)	-	-	↓	47-78	65(42-92.5)	68.2 (45.3 – 92.3)
TAT ($ng\,mL^{-1}$)	-	40.9 (13.75–61.45)	27.1 (16–54)	>15	-	34.4(18.2-63)	31.4 (17.8 – 54.5)
SF ($\mu g\,mL^{-1}$)	-	-	-	>100	-	124(21.9-274)	
SFMC ($\mu g\,mL^{-1}$)	-	-	-	-	-	-	119 (24.7 - 287)
PPIC($pmol\,L^{-1}$)	-	-	-	>1.5	-	-	1.40 (0.90 – 6.40)
F1+2 ($\mu g\,mL^{-1}$)	-	-	-	-	-	828(380-1400)	-
XDP($\mu g\,mL^{-1}$)					>2	-	-
PIC($\mu g\,mL^{-1}$)		3.23(1.31–8.7)					
tPAIC($ng\,mL^{-1}$)		21.1(10.45–36)					
sTM($TUmL^{-1}$)		24.7(13.2–37.4)					5.60 (4.08 - 7.73)
tPA($ng\,mL^{-1}$)			7.5 (6.4–10)				
PAI($ng\,mL^{-1}$)			100.6 (75–123.8)				

FDPs; fibrin related markers, AT; antithrombin, TAT; thrombin-antithrombin; SF, soluble fibrin, PPIC; plasmin-plasminogen inhibitor complex, F1+2; prothrombin fragment 1 and 2, XDP; X-oligomers, PIC;α2-plasmin inhibitor-plasmin complex, tPAIC; tissue plasminogen activator inhibitor complex, sTM; soluble thrombomudulin, t-PA; tissue plasminogen activator, PAI; plasminogen activator inhibitor

Different kind of hemostatic markers were measured depending on the purposes of the study. They were abnormal in DIC patients with solid cancer.

5.1.5 Laboratory Findings in Patients without DIC

Table 5.6 Global Coagulation Tests in Solid Cancer Patients without DIC

Parameters / Study	PT INR	Fg(mg dL^{-1})	PLT(10^9 L^{-1})
Sallah et al 2001	-	373(105-672)	214(56-921)
Kawasugi et al 2011	1.13 (1.03 – 1.24)	268 (189 – 372)	93 (67 – 161)

Fg; fibrinogen, PLT, platelet count

Fibrinogen and platelet count were slightly abnormal in solid cancer patients without DIC in Sallah et al. 2001 and Kawasugi et al. 2011 studies. PT INR values were normal to slightly abnormal according to Kawasugi et al. 2011.

Table 5.7 Hemostatic Markers in Solid Cancer Patients without DIC

Study \ Parameter	TAT($ng\,mL^{-1}$)	F1+2 ($pmol\,L^{-1}$)	sTM($TUmL^{-1}$)	FDP ($\mu g\,mL^{-1}$)	AT (%)	SFMC ($\mu g\,mL^{-1}$)	SF($\mu g\,mL^{-1}$)	PPIC ($\mu g\,mL^{-1}$)	D-dimer ($\mu g\,mL^{-1}$)
Kushimoto et al 2012	18.6 (10.1-30.3)	522 (350-813)					70.5 (55.1-95.7)	61.9 (15.2-222)	
Kawasugi et al 2011	19.6 (11.3 – 35.2)	-	4.85 (3.50 – 5.70)	23.3 (16.7 – 57.6)	70.0 (51.5 – 95.5)	78.8 (18.2 – 200)		2.30 (1.28 – 6.05)	12.0 (7.92 – 24.9)

TAT; thrombin-antithrombin; F1+2; prothrombin fragment 1+2, sTM; soluble thrombomudulin,
SFMC; doluble fibrin monomer complex, AT; antithrombin, PPIC; plasmin-plasminogen activator inhibitor complex, FDP; fibrin degradation products

Hemostatic markers results in solid cancer patients without DIC are abnormal compared to normal values.

5.1.6 DIC frequency:

Table 5.8 Frequency of DIC in Solid Cancer Patients

Study		N◦	DIC+(n)	DIC-(n)	frequency(%)
Sallah et al. 2001		1117	76	1041	6.8%
Aota et al. 2016		114	78	36	68.4%
Wada et al. 1999		86	65	21	75.6%
Kushimoto et al. 2012		132	48	84	36.4%
Okamoto et al. 2010		142	61	81	43%
Kawasugi et al. 2011	ISTH	143	46	97	32.2%
	JMHW		50	93	35%

The reported frequency of DIC in solid cancer is very different from a study to another, since it ranges from 6.8% to 75.6%.

5.1.7 Complications

Table 5.9 Clinical Complications in Solid Cancer Population

Complication / Study	Thrombosis	Bleeding	Metastasis	Other
S.Sallah et al 2001	36(lower extremity deep venous thrombosis 17, superficial thrombophelibitis 9, pulmunary embolism 4, pelvic and mesentric vein 4, renal 2)	109 episodes for 50 patients (venipuncture 38, skin and mucosal surfaces 26, hematuria 19, gastrointestinal 14, CNS 4, hemoptysis 8, after resection of tumor 1, chemotherapy 2)	35(46%)	Renal failure 14(21%) Acute respiratory distress syndome 9(12%) Liver failure 2 (3%)

CNS; central nervous system

Sallah et al. 2001 reported complications that occured in solid cancer patients with DIC.

5.1.8 Comparison of Laboratory Findings between DIC + and DIC – Groups:

Table 5.10 Comparison of Laboratory Findings between Solid Cancer Population with DIC and without DIC

Study	S.Sallah et al 2001		Kushimoto et al 2012		Kawasugi et al 2011	
Lab findings	DIC+	DIC-	DIC+	DIC-	DIC+	DIC-
PT INR	-	-	-	-	1.43(1.25–1.8)***	1.13(1.03–1.24)***
Fg(mg dL^{-1})	M:129	373			182(115–277)**	268 (189–372)**
PLT(10^{9} L^{-1})	52.5	214			42(25–77)***	93(67–161)***
SF(µg mL^{-1})	-	-	124(21.9-274)NS	61.9(15.2-222)	-	-
AT(%)	-	-	65.0(42.0-92.5)NS	70.5(55.1-95.7)	68.2(45.3–92.3)	70(51.5–95.5)
TAT(ng mL^{-1})	-	-	34.4 (18.2-63.0)**	18.6 (10.1-30.3)	31.4(17.8–54.5)	19.6(11.3–35.2)
F1+2(pmol L^{-1})	-	-	828 (380-1400)*	522 (350-813)	-	-
sTM(TUmL^{-1})	-	-	-	-	5.6(4.08-7.73)	4.85(3.5–5.7)
SFMC (µg mL^{-1})	-	-	-	-	119(24.7-287)	78.8(18.2–200)
PPIC (µg mL^{-1})	-	-	-	-	1.4(0.9–6.4)	2.3(1.28–6.05)
D-dimer (µg mL^{-1})	-	-	-	-	21.8(11.8–34.7)*	12.0 (7.92–24.9)*
FDP (µg mL^{-1})	-	-	-	-	40.4(27-72.1)**	23.3(16.7–57.6)**

AT; antithrombin, PLT; platelet count, TAT; thrombin-antithrombin; SF, soluble fibrin, PPIC; plasmin-plasminogen inhibitor complex, F1+2; prothrombin fragment 1 and 2, XDP; X-oligomers, PIC;α2-plasmin inhibitor-plasmin complex, tPAIC; tissue plasminogen activator inhibitor complex, sTM; soluble thrombomudulin, M; median

*** p<.001, ** p<.01, * p<.05

Significant differences between DIC and non DIC patients are observed in TAT (thrombin antithrombin), F1+2 (Prothrombin fragment 1+2), PIC (α2-plasmin inhibitor-plasmin complex), tPAIC (tissue plasminogen activator inhibitor complex) and sTM (soluble thrombomudulin) values according to Mei et al. 2019 and Kushimoto et al. 2012. Kushimoto et al. 2012 also reported that SF and AT levels were not significantly changed in DIC patients. In Kawasugi et al. 2011 study, significant changes in PT INR, platelet count as well as fibrinogen, FDP and D-dimer levels were observed in cancer patients with DIC.

1. **Comparison of Risk Factors between DIC+ and DIC- Groups**

Table 5.11 Comparison of Risk Factors between Solid Cancer Population with DIC and without DIC

Study		DIC+	DIC-	P value
S.Sallah et al 2001	No∘ patients	76	1041	
	Age			
	≤60	13	503	
	>60	63	538	.0001
	Sex			
	Male	52	565	.016
	Female	24	476	
	Cancer stage			
	Early	18	576	
	Advanced	58	462	.0001
	Vascular invasion	24	196	.0002
	Tumor necrosis	20	95	.0001
Aota et al 2016	Age	NS		>.05
	Sex ratio	NS		>.05
Kushimoto et al 2012	Sex ratio	NS		>.05

Sallah et al. 2001 found that age>60 and male gender may be independent factors that enhance the risk of developing DIC, but Aota et al. 2016 reported that there was no significant difference in the occurrence of DIC depending on age or sex ratio. Kushimoto et al. 2012 also reported that no significant differences were observed between male and female gender.

2. **Comparison between Complications in DIC+ and DIC- Groups**

Table 5.12 Comparison between Complications in Solid Cancer Patients with DIC and without DIC

Study		DIC+	DIC-
S.Sallah et al 2001	N◦ patients	76	1041
	Thrombosis	31(40.8%)	
	Bleeding	50(65.8%)	
	Metastasis	Liver: 35(46%)	Liver: 250(24%)
	End organ damage		
	Renal failure	14(18%)	
	Acute respiratory distress syndrome	9(12%)	
	Liver failure	2(3%)	

Sallah et al. 2001 reported that bleeding occurred more frequently than thrombosis in DIC patients, and that the percentage of patients with liver metastasis were more important in the DIC group.

5.2 Group 2: Hematological Malignancies

5.2.1 Patients' Characteristics

Table 5.13 Epidemiologic Data in Patients with Hematological Malignancies in Selected Articles

Study	No patients	Age	Sex (F:M)	Study design
Dixit et al. 2007	67	25(3-64)	8/19	Cohort study
Kawasugi et al. 2011	148	62(45-73)	65/83	Cohort study
Wada et al. 1999	114			Cohort study
Yanada et al. 2006	125	16-83	39/86	Cohort study
Mei et al. 2019	104	51 (34–59.75)	40/64	Cohort study
Okajima et al. 2000	258			Cohort study
Okamoto et al. 2010	115	62(45-73)	50/65	Cohort study
Sletnes et al. 1995	50	14-69	30/20	Cohort study
Kushimoto et al. 2012	152	62(45-72)	67/85	Cohort study
Asakura et al. 2001	52			Case-control study

F; female, M; male

Number of patients vary from one study to another, with a male predominance and an age that range from 3 to 83 years old. Most of the studies are cohort.

5.2.2 Distribution of Population According to Cancer Type

Table 5.14 Type Of Cancer in the Population with Hematological Malignancies

Type / Study	ALL	AML	CML	MDS	NHL	Global HM
Dixit et al 2007	+	+				
Kawasugi et al 2011						+
Wada et al 1999						+
Yanada et al 2006	+	+		+		
Mei et al 2019						+
Okajima et al 2000						+
Okamoto et al 2010						+
Sletnes et al 2009	+	+				
Asakura et al 2001	+	+	+		+	
Kushimoto et al 2012						+

ALL, acute lymphoblastic leukemia, AML, acute myeloblastic leukemia, CML; chronic myeloid leukemia, MDS; myelodisplastic syndrome, NHL; non-hodgkin lymphoma, HM; hematological malignancies

Dixit et al. 2007, Yanada et al. 2006 and Sletnes et al. 1995 et al included a population of acute leukemia while the other studies included population with underlying diseases known to be associated with DIC. And in Asakura et al. 2001 all patients already had DIC.

5.2.3 Diagnostic Criteria

Table 5.15 DIC Diagnostic Criteria Used in Different Studies

Study	Diagnostic criteria
Dixit et al 2007	Modified ISTH critera
Kawasugi et al 2011	Overt ISTH 3.6 / JMHW criteria 3.4
Wada et al 1999	Modified JMHW criteria A.1
Yanada et al 2006	Overt ISTH criteria
Mei et al 2019	Overt ISTH criteria
Okajima et al 2000	Underlying disorders frequently associated with DIC (+); (+)SFMC + ↑ FDP ($>$ 500ng mL^{-1}); and/or (+)clinical bleeding/organ failure
Okamoto et al 2010	Modified JMHW criteria
Sletnes et al 1995	1+2, or 1+3, or all: 1. ↓ Fg (1.6 g L^{-1}) or 50% reduction in 24h). 2. ethanol gelation test (+) 3. ↑ (SFMC), D-dimer.
Kushimoto et al 2012	Overt ISTH criteria
Asakura et al 2001	JMHW Criteria

SFMC; soluble fibrin monomer complex, FDPs; fibrin related markers, Fg, fibrinogen

Different criteria were used depending on the country, population and the purpose of the study.

5.2.4 Laboratory Findings in DIC Patients

Table 5.16 Global Coagulation Tests in DIC Patients

Parameter / Study	HM	PT(sec)	aPTT(sec)	TT(sec)	Fg(mg/dL)	PLT($10^4\mu L^{-1}$)
Kawasugi et al 2011	HM	ratio:1.30(1.15–1.44)	-	-	256 (109–345)	3,5(1,8-4,7)
Yanada et al 2006		1,2(0,96-1,48)	-	-	284(71-847)	4.2(1.8-16.5)
Dixit et al 2007	ALL	22.7 ± 5.3	42.5 ± 14.0	20.0 ± 3.4	296.3 ± 88.3	4.6 ± 5.18
	AML	17.2 ± 1.2	30.2 ± 6.2	17.6 ± 1.9	386.2 ± 43.0	2.25 ± 1.66
Asakura et al 2001	APL	15.5(14.4-16.3)	-	-	106(57–117)	3.8(2.2–4.6)
	CML	15.5(15.0–16.1)	-	-	135(114–148)	4.3(3.9–5.7)
	NHL	14(12.3–14.6)	-	-	303(277–331)	10.2(7.2–14.4)
	AL(-APL)	13.4(13.0–14.5)	-	-	205(160–303)	4.6 (2.4–11.0)

PT; prothrombin time, aPTT; activated partial thromboplastin time, TT; thrombin time, PLT; platelet count, APL; acute promyelocytic leukemia, AL(-APL); acute leukemia except APL, CML, chronic myelogeneous leukemia, NHL, non-Hodgkin lymphoma, TT; thrombin time, HM; global hematological malignancies, * * *p<.001, **p<.01, *p<.05

Studies have shown that there were abnormal changes in screening tests in DIC patients with hematological malignancies.

Table 5.17 Hemostatic Markers in DIC Patients

HM / Study		FDP ($\mu g\,mL^{-1}$)	D-dimer ($\mu g\,mL^{-1}$)	AT (%)	PAI ($ng\,mL^{-1}$)	sTM ($TUmL^{-1}$)	SFMC ($\mu g\,mL^{-1}$)	tPAIC ($ng\,mL^{-1}$)	XDP ($\mu g\,mL^{-1}$)	SFM ($\mu g\,mL^{-1}$)	TAT ($ng\,mL^{-1}$)	PPIC ($\mu g\,mL^{-1}$)	F1+2 ($pmol\,L^{-1}$)
Kawasugi et al 2011	HM	40.6 (27.6–69.5)	21.4 (10.1–45)	84.2 (69.9–101)	-	4.7 (2.7–6.8)	198 (38.8-300)	32.2 (16.8–30)	-	-	32.2(16.8-30)	7.5 (2.75–13.6)	-
Mei et al 2019	HM	-	-	-	-	18.8 (11.75-25.2)		8.6 (5–16.88)			21.1 (7.48–43.43)	3.51 (1.36–9.4)	-
Okajima et al 2000	HM	-	-	-	-	-	-	-	25	-	35	7.5	-
Yanada et al 2006	HM	47,7(11,2–307)		-	-	-	-	-	-	-	-	-	
Kushimoto et al 2012	HM	-	-	-	88(70.4-101)	-	-	-	-	240(42.6-300)	31(17-90)	-	1060(571-1400)
Asakura et al 2001	APL	96.3(69–133.8)		-	28.3 (22.4–43.4)	-	-	4.6 (3.4–5.7)	-	-	41.2 (18.7–58)	10.8 (6.6–13)	-
	AL(-APL)	41.2(24.9–73.1)		-	85.8(50.6–185.5)		-	8.6(5.9–15.1)		-	15.8 (8.5–28.6)	3.2 (1.4–4.6)	-
	CML	31(22.4–41)		-	244(236.0–262.1)		-	31.5(21.6–37)		-	13.9 (10.4–37.5)	1.5 (0.7–2.9)	-
	NHL	28.8(22.8–47)		-	107.6(65.1–271.5)		-	13.2(7.9–14.8)		-	16 (8.8–20.8)	1.7 (0.6–3.2)	-

FDPs; fibrin degradation prducts, AT; antithrombin, PAI; plasmin-activator inhibitor, sTM; soluble thrombomodulin, SFMC; Soluble fibrin monomer complex, tPAIC, tissue plasminogen activator inhibitor complex, XDP; X oligomers, SFM, soluble fibrin monomers, TAT, thrombin-antithrombin complex, PPIC, plasmin-plsminogen inhibitor complex, F1+2; prothrombin fragments 1+2, HM; hematological malignacies, APL; acute promyelocytic leukemia, AL(-APL); acute leukemia except APL, CML; chronic myeloid leukemia, NHL; non-Hdgkin lymphoma , * * *p<.001 **p<.01 *p<.05

All studies showed that levels of hemostatic markers were abnormal in all DIC patients, with the exception of AT levels which were in the normal range.

5.2.5 Laboratory Findings in non-DIC Patients

Table 5.18 Global Coagulation Tests in Non-DIC Patients

Parameters / Study	Kawasugi et al 2011	Wada et al 1999	Yanada et al 2006	Dixit et al 2007	
				ALL	AML
PT(sec)	ratio 1.09 (1.03 – 1.15) 8/96 (8.3%)		1,13(0,9-1,44)	14.7 ± 1.3	15.6 ± 1.5
aPTT (sec)				30.3 ± 2.0	29.7 ± 2.0
TT (sec)				17.7 ± 1.2	17.7 ± 1.2
Fg ($mg\,dL^{-1}$)	317(193 – 439) 1/96 (1%)	300 ± 149	4,01(1,49-7,99)	365.5 ± 59.2	375.7 ± 57.0
PLT ($10^4 \mu L^{-1}$)	6,4(3,7-11,0)67/96 (69,8%)	6.2 ± 5.6	59(3-1700)	365.5 ± 59.2	49.8 ± 39.9

PT; prothrombin time, aPTT; activated partial thromboplastin time, TT; thrombin time, PLT; platelet count, ALL; acute lymphoblastic leukemia, AML; acute myeloblastic leukemia

Studies found that screening tests for non-DIC patients were abnormal, with the exception of fibrinogen levels which were in the normal range.

Table 5.19 Hemostatic Markers in Non-DIC Patients

Parameters / Study	Kawasugi et al 2011	Wada et al 1999	Yanada et al 2006	Dixit et al 2007		Kushimoto et al 2012
					ALL	AML
FDP ($\mu g\,mL^{-1}$)	19 (10.1 – 30.8) 720/960 (75%)	11.9 ±7.8	5,0(1,4-25,3)			
AT (%)	91 (75.2 – 102)	90.1 ± 21.1		83.0 ± 9.6	77.5 ±12.5	91.0 (76.3-103)
D-dimer ($ng\,mL^{-1}$)	10.6 (5.17 – 21.9)	1120 ± 1187				
sTM ($mg\,mL^{-1}$)	3.65 (2.70 – 6.20)					
TAT ($ng\,mL^{-1}$)	11.7 (7.3 – 30.4)	15.5 ± 17.6				9.50 (4.83-23.9)
PPIC ($mg\,mL^{-1}$)	2.60 (1.50 – 5.05)	1.9 ± 2.2				
SFMC ($\mu g\,mL^{-1}$)	45.0 (10.5 – 182)					
SFM ($\mu g\,mL^{-1}$)		58.9 ± 61.8				18.5 (7.05-91.7)
F1 +2 ($pmol\,L^{-1}$)						506 (243-774)

FDP; fibrin degradation products, AT; antithrombin, sTM; soluble thrombomodulin, TAT;thrombin-antithrombin, PPIC; plasmin-plasminogen inhibitor complex, SFMC; soluble fibrin monomer complex, SFM; soluble fibrin monomer, F1+2; prothrombin fragment 1+2,
ALL; acute lymphoblastic leukemia, AML; acute myeloblastic leukemia

Studies reported that hemostatic markers levels were abnormal in non DIC patients except for AT levels which were normal.

5.2.6 DIC Frequency

Table 5.20 DIC Frequency in Patients with Hematological Malignancy

Study	Okajima et al 2000	Yanada et al 2006	Dixit et al 2007	Sletnes et al 2009	Kushimoto et al 2012	Wada et al 1999	Okamoto et al 2010
Frequency	10.10%	29%	14.9%	20%	41.4%	65.14%	52.63%

The frequency varies in these studies from 10.10% to 65.14%.

5.2.7 Complications

Table 5.21 Complications in Patients with Hematological Malignancies

Study / Complication	Okajima et al 2000	Dixit et al 2007	Sletnes et al 2009	Asakura et al 2001
Bleedin	≈ 50%(DIC)	60%(DIC)	100%	-
Organ failure	≈20%	-	-	12/52(40.4%)
Sepsis				13/52(25%)

These studies reported that complications in DIC patients were bleeding, organ failure and sepsis.

5.2.8 Comparison between DIC and non-DIC patients

Table 5.22 Comparison between laboratory findings in DIC+ and DIC- patients

Parameter / Study	Kawasugi etal 2011		Yanada etal 2006		Dixit et al 2007				Kushimoto etal 2012	
					ALL		AML			
	DIC+	DIC-	DIC+	DIC-	DIC+	DIC-	DIC+	DIC-	DIC+	DIC-
PT ratio	1.30 (1.15–1.44) $***$ 30/52 (57.7%)	1.09 (1.03–1.15) $***$ 8/96 (8.3%)	1,2 (0,96-1,48)$*$	1,13 (0,9-1,44)	22.7 $\pm$5.3$**$	14.7 $\pm$1.3	17.2 $\pm$1.2$*$	15.6 $\pm$1.5		
aPTT					42.5$\pm$14$*$	30.3 $\pm$2.0	30.2 $\pm$6.2	29.7 $\pm$2.0		
TT					20 $\pm$3.4	17.7 $\pm$1.2	17.6 $\pm$1.9	17.7 $\pm$1.2		
Fg(mg dL^{-1})	256 (109–345) $**$ 10/52 (19.2%)	317 (193–439) $**$ 1/96 (1.0%)	2,84 (0,71-8,47)$*$	4,01 (0,49-7,99)	296.3 $\pm$88.3	365.5 $\pm$59.2	386.2 $\pm$43.0	375.7 5$\pm$7.0		
PLT(10^4 μL^{-1})	3,5 (,8-4,7)$***$ 49/52 (94,3%)	6,4 (3,7-11,0)$***$ 67/96 4(69,8)	4.2 (1.8-16.5)	5.9 (0.3-170)	4.6 $\pm$5.18$*$	6.91 $\pm$4.92	2.25 $\pm$16.6	4.98 $\pm$3.99		
FDP(μg mL^{-1})	40.6 (27.6–69.5) $***$ 51/52 (98.1%)	19 (10.1–30.8) $***$ 72/96 (75%)	47,7 (11,2-307)$***$	5,0 (1,4-25,3)	-	-	-	-	-	-
AT(%)	84.2 (69.9–101) $***$	91 (75.2–102) $***$			83.3 $\pm$15.2	83 $\pm$9.6	91.2 $\pm$20.1	77.5 $\pm$12.5	88 (70.4-101)	91 (76.3-103)
D-dimer (ng mL^{-1})	21.4 (10.1–45) $***$	10.6 (5.17–21.9) $***$	-	-	-	-	-	-	-	
TAT(ng mL^{-1})	32.2 (16.8–30) $***$	11.7 (7.3–30.4) $***$	-	-	-	-	-	-	31 (17-90)$***$	9.5 (4.83-23.9)

PPIC($\mu g\,mL^{-1}$)	7.5 (2.75–13.6) $***$	2.6(1.5–5.05) $***$	-	-	-	-	-	-	-	-
SFMC($\mu g\,mL^{-1}$)	198 (38.8-300) $**$	45 (10.5–182) $**$	-	-	-	-	-	-	-	-
sFM($\mu g\,mL^{-1}$)	-	-	-	-	-	-	240 (42.6-300)	18.5 (7.05-91.7)	240 (42.6-300)$***$	18.5(7.05-91.7)
F1+2($pmol\,mL^{-1}$)	-	-	-	-	-	-	-	-	1060 (571-1400)$***$	506 (243-774)

PT; prothrombin time, aPTT; activated partial thromboplastin time, TT; thrombin time, PLT; platelet count, Fg; fibrinogen, FDPs; fibrin degradation prducts, AT; antithrombin, PAI; plasmin-activator inhibitor, sTM; soluble thrombomodulin, SFMC; Soluble fibrin monomer complex, tPAIC, tissue plasminogen activator inhibitor complex, XDP; X oligomers, SFM, soluble fibrin monomers, TAT, thrombin-antithrombin complex, PPIC, plasmin-plsminogen inhibitor complex, F1+2; prothrombin fragment 1+2, HM; hematological malignacies, APL; acute promyelocytic leukemia, AL(-APL); acute leukemia except APL, CML; chronic myelocytic leukemia, NHL; non-Hdgkin lymphoma , $***p<.001$ $**p<.01$ $*p<.05$

Studies found that there were significant differences in laboratory finding (TAT, plasmin-plsminogen inhibitor complex (PPIC), sTM, and tissue plasminogen activator inhibitor complex (tPAIC), D-dimer, SFMC, PT ratio, fibrinogen, SF, and prthrombin fragments 1+2 and FDP levels between patients with DIC and those with non DIC in hematological malignancies. Dixit et al. 2007 found that in ALL patients there were significant differences in the mean platelet count, fibrinogen, PT, aPTT with DIC patients compared to those without DIC. There was no difference in AT levels between the groups. And they found that in AML patients there were significant difference in the mean platelet and PT with DIC group than in the non-DIC group; however, there was no significant difference with respect to fibrinogen, TT, or AT levels.

5.2.9 Comparison between Risk Factors in DIC+ and DIC- Groups

Table 5.23 Comparison between Risk Factors in DIC+ and DIC- Patients:

Study / RF	Dixit et al 2007						Yanada et al 2006			Kushimoto et al 2012		
	AML			ALL								
	DIC+	DIC-	P	DIC+	DIC-	P	DIC+	DIC-	P	DIC+	DIC-	P
Age	23.7 ±10.5	33.3 ±12.0	>,05	26 ±13.5	20.8 ±13.8	>.05	45.5 (16–83)	52 (16–79)	0.3994			
Sex(F:M)							24/12	62/27	0.8318	36/27	50/40	>.05

ALL; acute lymphoblastic leukemia, AML; acute myeloblastic leukemia

Studies found that there was no significant difference between the 2 groups with respect to age, and no significant differences were observed between male and female gender.

5.2.10 Comparison between Complications in DIC+ and DIC- Groups

Table 5.24 Comparison between Complications in DIC and non DIC Patients

Study / Complication	Okajima et al 2000		Dixit et al 2007						Sletens et al 2009		
			AML			ALL					
	DIC+	DIC-	DIC+	DIC-	P	DIC+	DIC-	P	DIC+	DIC-	P
Bleeding	+		+	+	<.05	+	+	NS	+	+	<.001
Organ failure	+										

AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia

Dixit et al. 2007 found that the presence of DIC was not associated with significant bleeding manifestations compared to the non-DIC group in ALL patients, but in AML patients, it was more commonly associated with severe bleeding. Sletnes et al. 1995 found that the proportion of patients with major bleeding was significantly greater among the DIC patients (6/10 vs 3/40, p <.OO1).

5.3 The Relevance of using Scores in the Diagnosis of DIC

According to Conditions 1999 and Levi et al. 2009, the combination of tests results in patients that are likely to have DIC can give reliable results with reasonable certainty.

Table 5.25 Diagnostic Criteria for DIC Established by the Japanese Ministry of Health and Welfare

Laboratory tests	Points
Global coagulation	>80 but ≤120; 1 point
tests	(within 24 hours ≥30% reduction; 2 point)
Platelet counts	>50 but ≤80; 2 points
($10^3 mL^{-1}$)	(within 24 hours ≥30reduction; 3 point)
	≤50; 3 points
Fibrin-related marker	≥10 but <20; 1 point
(FDP,$\mu g\, mL^{-1}$)	≥20 but <40; 2 points
	≤40; 3 points
Fibrinogen ($g\, L^{-1}$)	>1 but ≤1.5; 1 point
	≤1; 2 points
PT (PT ratio)	≥1.25 but <1.67; 1 point
	≥1.67; 2 points
New Markers	≥70; 1 point
Antithrombin (%)	≥2-fold the upper limit of
TAT complex or SF or SFMC	the normal range
Liver function	(Liver failure) -minus 3 points
Diagnosis of DIC	≥6 points

5.3.1 Comparison between Global Coagulation Tests and Scores

1. **Group 1a**

Patients' Characteristics

Table 5.26 Patients' Characteristics in the Selected Study

study	N ∘	Age	Sex(F:M)	Type of the study
Aota et al. 2016	114 (c) 62(o)	51.5-72	83:150	cohort Study

c; cancer patients, o; other diseases

The studied population mainly had cancer. We divided patients into 2 groups: solid cancer and other diseases. Age ranged from 51.5 to 72 years with a male predominance.

Underlying Diseases Associated with Patients

Table 5.27 Patients' Distribution According to the Underlying Disease

Disease \ Study	Aota et al 2016
Stomach cancer	32
Lung cancer	27
Liver cancer	9
Pancreatic cancer	6
Bile duct cancer	6
Unknown cancer	5
Breast cancer	5
Prostate cancer	5
Other cancers	19
Organ failure	24
Obstetrics diseases	7
Trauma	6
Others	28
Total	174

The predominant disease observed in the studied population is solid cancer, and a large range of solid cancer types were studied.

Diagnostic Criteria

Table 5.28 DIC Diagnostic Criteria Used in the Selected Study

	N ○	Diagnostic criteria
Aota et al 2016	174	JMHW diagnostic criteria 5.25

Aota et al. 2016 used JMHW criteria to diagnose DIC.

Distribution of Patients According to the Diagnosis of DIC

Table 5.29 Patients Diagnosed with non-DIC and DIC by the JMHW Scoring System

	Non DIC	DIC
Stomach cancer	9	23
Lung cancer	10	17
Liver cancer	2	7
Pancreatic cancer	0	6
Bile duct cancer	1	5
Unknown cancer	1	4
Breast cancer	2	3
Prostate cancer	2	3
Other cancers	9	10
Organ failure	11	13
Obstetrics diseases	3	4
Trauma	2	4
Others	11	17
Total	63	116

Comparison between Global Tests and Scores

Table 5.30 Comparison between the use of global coaguation tests and JMHW scoring system to diagnose DIC

Tests	AUC	Cutoff(Pts)	Sensitivity(%)	Specificity(%)	(+)PV(%)	(-)NPV(%)
① GCT	0.965	4.0	68.3	98.3	95.6	85.1
② GCT +reduced PLT	0.976	5.0	96.8	91.4	85.9	98.1
③ GCT + reduced PLT + AT + SF/TAT complex (JMHW scoring system)	0.989	6.0	98.4	94.8	91.2	99.1

GCT; global coagulation tests(prothrombin time + fibrinogen level + fibrin-related markers level), +PV; positive predictive value, -PV; negative predictive value, AUC, area under the curve, PLT, platelet count, AT; anti-thrombin, SF/TAT, soluble fibrin or thrombin anti-thrombin complex

Aota et al. 2016 compared between the relevance of global coagulation tests alone and the combination between them and specific markers to diagnose DIC. Global tests and the combination of global tests and specific markers were given cutoff points in order to explore the diagnosis capacity of each part (①,②,③)

2. **Group 2: Hematological Malignancies**

Patients' Characteristics

Table 5.31 Study Characteristics

	N ◦	Age	Sex(F:M)	Study design
Aota et al 2016	274	39-63	127:147	Cohort study

The study comprised adult population with an age less than 63 years, and the predominant gender was the male one.

Patients' Distribution According to the Type of Hematological Malignancy

Table 5.32 Patients' Distribution According to the Type of Hematological Malignancy

Disease \ Study	Aota et al 2016
AML	78
APL	49
NHL	48
ALL	65
CML/CMLbc	12
AMMoL/AMoL	10
PNH	5
Multiple myeloma	5
MDS	2

AML, acute myeloblastic leukemia; APL, acute promyelocytic leukemia; NHL, Non-Hodgkin lymphoma, ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CMLbc,CML blast crisis,AMMoL, acutemyelomonocytic leukemia;AMoL, acutemonocytic leukemia; PNH, paroxysmal nocturnal hemoglobinuria.

The predominant disease observed in the studied population is leukemia.

Diagnostic Criteria

Table 5.33 DIC Diagnostic Criteria Used in the Selected Study

	N ◦	Diagnostic criteria
Aota et al 2016	174	JMHW diagnostic criteria 5.25

Patients' Distribution According to the Diagnosis of DIC

Table 5.34 Patients Diagnosed with non-DIC and DIC by the JMHW Scoring System

	Non DIC	DIC
AML	31	33
APL	21	28
NHL	20	24
ALL	24	25
CML/CMLbc	2	7
AMMoL/AMoL	4	4
PNH	1	2
Multiple myeloma	2	2
MDS	2	0
Total	107	125

AML, acute myeloblastic leukemia; APL, acute promyelocytic leukemia; NHL, Non-Hodgkin lymphoma, ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CMLbc,CML blast crisis,AMMoL, acutemyelomonocytic leukemia;AMoL, acutemonocytic leukemia; PNH, paroxysmal nocturnal hemoglobinuria.

The patients' diagnosis with DIC is higher than the patients with non-DIC.

Comparison between Global Tests and the Score

Table 5.35 Comparison Between the Use of Global Coagulation Tests and JMHW Scoring System to Diagnose DIC

Tests	AUC	Cutoff(Pts)	Sensitivity(%)	Specificity(%)	(+)PV(%)	(-)NPV(%)
① GCT	0.985	2	66.4	99.2	98.6	77.4
② GCT + AT + SF/TAT complex (JMHW scoring system)	0.979	4	97.2	96.0	95.4	97.6

GCT; global coagulation tests(prothrombin time + fibrinogen level + fibrin-related markers level + platelet count), +PV; positive predictive value, -PV; negative predictive value, AUC, area under the curve, AT; anti-thrombin, SF/TAT, soluble fibrin or thrombin anti-thrombin complex

In the diagnosis of DIC vs non-DIC, the cutoff DIC scores for (GCT) were 2 and those for (GCT+AT+SF or TAT) were 4. (GCT + AT+ SF or TAT) showed the highest sensitivity (97.2), while (GCT) showed the highest specificity (99.2).

5.3.2 Comparison between Scoring Systems

Patients' Characteristics

Table 5.36 Patients' Characteristics

study	No	Age	Sex ratio (F/M)	Study design
Takemitsu et al 2011	413	64(49-73)	173/242	cohort study
M,Wang et al 2015	619		277/342	cohort study
K. Kawasugi et al 2011	692			cohort study
Luo 2019	1318	18-70	478/598	cohort study
Wada et al 2003	1284			cohort study

The number of patients varies from study to study with male predominance and all studies are cohorts.

Patients' Distribution According to the Underlying Disease

Table 5.37 Different Underlying Diseases in the Studies

Study	Takemitsu et al. 2011	Wang et al. 2015	Kawasugi et al. 2011	Luo et al. 2019	Wada et al. 2003a
Solid cancer	+	+	+	+	+
Haematopoietic tumor	+	+	+	+	+
Infectious disease	+	+	+	+	+
Aneurysm (vascular anomalies)	+	+	+	+	
Trauma	+	+	+	+	+
Cardiovascular disease	+		+	+	
Gastrointestinal disease	+		+		
Autoimmune disease	+	+		+	
Obstetrics disease	+	+		+	
Chock		+		+	
Liver diseases	+			+	

Different underlying diseases were included in the selected studies.

Diagnostic Rate

Table 5.38 Diagnostic Rate for DIC Patients:

Study	Takemitsu et al 2011						Wang et al 2015						Kawasugi et al 2011						luo 2019			
Score	JMHW		ISTH		JAAM		JMHW		ISTH		JAAM		CDSS		JMHW		ISTH		JMHW		ISTH		CDSS	
Dg rate%	SC	HM	SC	HM	SC	HM	SC	HM	SC	HM	SC	HM	SC	HM	SC	HM	SC	HM	SC	HM	SC	HM	SC	HM
	34,6	41,5	33,1	31,9	69,9	75,5	56,25	52,42	43,75	50	65,63		59,31	49,19	35	46,6	32,2	35,1	40	72,4	40	71,5	48,3	58,5

SC; solid cancer, HM; hematological malignancy

In the hematological malignancies, group JMHW had the highest diagnostic rate in most studies, in solid cancer group. In Wang et al. 2015 , Takemitsu et al. 2011 JAAM had the highest diagnostic rate while Luo et al. 2019 found that CDSS had the highest diagnostic rate.

Concordance Rate

Table 5.39 Concordance Rate between Scores

study	wada et al 2003		Luo 2019			
population	HM	nn HM	HM		nn HM	
score	ISTH vs JMHW	ISTH vs JMHW	CDSS vs ISTH	CDSS vs JMHW	CDSS vs ISTH	CDSS vs JMHW
concordance rate	64,80%	69,20%	80%	76,90%	81,70%	84,70%

HM; hematological malignancy, nn HM; non hematological malignancy

Wada et al. 2003b and Luo et al. 2019 found that the concordance rate is higher in patients with non-hematological malignancy than in those with hematological malignancy.

Prognostic Values

Table 5.40 Prognostic Values of Scoring Systems:

Study	Takemitsu et al 2011			Wang et al 2015						Luo 2019						Kawasugi et al 2011					
Score	JMHW	ISTH	JAAM	JMHW		ISTH		JAAM	CDSS	JMHW		ISTH		CDSS		JMHW		ISTH			
Population	all	all	all	HM	nn HM	HM	nn HM	nn HM	HM	HM	nn HM	HM	nn HM	HM	nn HM	SC	HM	SC	HM		
mortality for DIC	35,5	40,60	31,7	36.07	47.8	33.08	43.81	38.82	36.07	33,80	55,40	32,9	53,5	36,	54,5	30,00	24,60	30,40	30,80		
Sensitivity for death	51.3	50.4	80	80	47.8	78.18	43.81	38.82	80	85.9	74.3	82.6	71.3	75	81.2%	-	-	-	-		
Specificity for death	64.9	71.4	33.2	59.59	66.80	54.92	56.40	37.60	59.59	32.9	78.0	32.9	75.1	48.1	77.3	-	-	-	-		

In Takemitsu et al. 2011 et al study, ISTH had the highest mortality rate, JAAM had the highest sensitivity for death while ISTH had the hight specificity. In hematological malignancy, Wang et al. 2015 and Luo et al. 2019 found that CDSS had the highest mortality rate ,JMHW had the highest sensitivity for death while LMHW and CDSS had the highest specificity. In non-hematological malignancy, M,Wang et al and l,luo et al found that JMHW had the highest mortality rate, JMHW had the highest specificity for death and JMHW and CDSS had the highest sensitivity for death. In hematologiacal malignancy and solid cancer, Kawasugi et al. 2011 found that ISTH had the highest mortality rate.

5.4 Cancer and pre-DIC

Pre-DIC, or non-overt DIC, is defined as a state where decompensated DIC has not been reached yet, and where hemostatic abnormalities are more subtle than in the overt state Lee and Song 2010.

Kaneko and Wada 2011 reported that in a retrospective study, they found that 80% of patients displayed remission of DIC when early treatment was initiated, while a higher number of cases worsened when treatment was begun with and elevated score.

5.5 Scores and Non-overt DIC

Table 5.41 Overt DIC and Modified Diagnostic Criteria for Non-Overt DIC to Detect DIC or Pre-DIC State

Overt-DIC criteria			Modified non-overt-DIC diagnostic criteria			
	Point	Present data	Point	Change of data[a]	Point	Score
Platelet counts ($10^9 L^{-1}$)	0	>100	0	>50% of reduction	1	
	1	>50 but <100	1	>50% of reduction	1	A
	2	<50	2		0	
FDP ($mg\,L^{-1}$)	0	<10	0	5 times of increase	1	
	2	>10 but <25	1	5 times of increase	1	B
	3	25>	2		0	
Fibrinogen ($g\,L^{-1}$)	0	>1	0	>50% of reduction	1	
	1	<1	1	>50% of reduction	1	C
	2	–	2		0	
PT (sec)[b]		<14.0	0	Prolongation: > 2.0	1	
	1	>14.0 but <17.0	1	Prolongation: > 2.0	1	D
	2	>17.0	2		0	
AT	–	–		AT <70% 1 point		E
FMC or TAT	–	–		FMC >10 $mg\,L^{-1}$ or TAT >10 $\mu g\,L^{-1}$ 1 point		F
Diagnosis of DIC		or >5 points		Diagnosis of DIC and pre-DIC: A 1 B 1 C 1 D 1 E 1 F 5 or > 5		

Diagnostic Criteria

Table 5.42 Diagnostic Criteria for overt DIC and non-overt DIC by ISTH and Modified non-overt ISTH

Overt DIC		Non-overt DIC	
		By original ISTH criteria	By modified ISTH criteria
Platelet count (μL^{-1})	Increase: -1 point	Only decrease: 1 point	
50,000-100,000 : 1 point	Decrease: 1 point	($<$ 100,000)	
$<$50,000 : 2 point			
PT (s)	Prolongation of PT	Not prolonged: -1 point	Only prolonged: 1 point
	3-6 : 1 point	Prolonged: 1 point	($>$3 s)
	$\geq$6 :2 point		
Fibrinogen ($mg\,dL^{-1}$) 100 : 1 point	+ Underlying disorder associated with DIC: 2 points +		
D-dimer ($\mu g\,mL^{-1}$)	0.5-1 : 1 point	Not increase: -1 point	Always increase: 1 point
	1-3 : 2 point	Increased: 1 point	($\geq$0.5)
	$\geq$3 : 3 point		
Protein C activity (%)		Normal: -1 point	Decrease: 1 point
		Decreased: 1 point	($<$70)
Antithrombin III (%)		Normal: -1 point	Decrease: 1 point
		Decreased: 1 point	($<$80)
Total	$\geq$5 points	$\geq$5 points	(2 +)

Table 5.43 Study Characteristics and Design

	N ∘	Age	Sex(F:M)	Study design
Toh, Downey 2005	516	M: 61	227:289	Cohort study
Wada et al 2010	613	29-84.6	240:373	Cohort study
Lee, Song 2010	296	M 64	126:170	Cohort study

M; median

All studies were cohorts, with an adult population and a male predominance.

Underlying Diseases of the Studied Population

Table 5.44 Distribution of Population according to Underlying Diseases

Study / UD	Toh, Downey 2005 n(%)	Wada et al 2010	Lee, Song 2010
Sepsis	140(27%)	219 (35.7%)	83(28%)
Solid cancer	26(5%)	142 (23.1%)	41(14.2%)
Hematopoietic Tumor		115 (18.7%)	
Trauma	93(18%)	23(3.7%)	77(26.6%)
Severe hepatic failure	77(15%)		
Liver diseases		5(0.8%)	4(1.4%)
Pancreatitis	77(15%)		
Aneurysm	77(15%)	29 (4.7%)	
Graft rejection	10(1.6%)		
Obstetric diseases		7 (70.0%)	4(1.5%)

UD; underlying disease

Different underlying diseases were included in the selected articles.

Diagnostic Criteria

Table 5.45 Diagnostic Criteria for non-overt and overt DIC

Toh, Downey 2005		Wada et al 2010		Lee, Song 2010	
DIC	N/o DIC	DIC	N/o DIC	DIC	N/o DIC
N/o ISTH + clinical signs	N/o ISTH	overt criteria 5.41	N/o criteria 5.41	overt ISTH +clinical signs	N/o ISTH Modified N/o ISTH 5.42

N/o DIC; non-overt DIC

Non overt DIC were diagnosed by modified diagnostic criteria and ISTH non-overt DIC scoring system in selected studies. Overt DIC were diagnosed by overt diagnostic criteria in Wada et al. 2010 study, and using ISTH overt DIC in Toh and Downey 2005 study.

Diagnosis of non-overt, overt and non DIC

Table 5.46 Patients Diagnosed with non-DIC, non-overt DIC and DIC

	No	Dg criteria	Non DIC	Non overt DIC	Overt DIC
Toh et al 2005	450	N/o ISTH	311	90	49
Wada et al 2010	613	Overt criteria	388		225
		M N/o criteria		286	
Lee, Song et al 2010	289	N/o ISTH	150	116	30
		M N/o ISTH	134	125	

More patients were diagnosed with non overt-DIC than overt DIC according to previous studies.

Death Rate

Table 5.47 Death Rate in non-Dic, non-overt DIC and overt DIC Patients

	No◦	Non-DIC n(%)	Non-overt DIC	Overt Dic
Toh,Downey 2005	175/450	-	70/90 (77.8%)	38/49 (77.6%)
	22/66	-	11/22 (50%)	6/11(55%)
Wada et al 2010	139/613	44/322 (13.7%)	94/286 (32.9%)	68/181 (37.6%)
Lee, Song 2010	49/296	10(7.5%)♯	27(21%)♯	12(40%)

♯; same death rate in both diagnostic criteria

Death rate is different between non-DIC group and non-overt DIC group, and between non-overt DIC and overt DIC. In Toh et al. 2016 study, they are the same.

Sensitivity and Specificity for Death

Table 5.48 Sensitivity and Specificity for Death of Scoring Systems in non-overt DIC Patients

	Dg criteria	Sensitivity	Specificity	(+)Predictive value	(-)Predictive value	95%CI
Toh, downey 2005		40% (33–47%)	93% (89–95%)	78% (68–85%)	71%(66–75%)	
Wada et al 2010		67.6%	40.5%	32.9%	67.13%	
Lee, Song 2010	N/o ISTH	73%	61.1%			
	M N/o ISTH	73%	55.9%			

Dg; diagnostic, N/o; non-overt

Sensitivity and specificity for death are heterogeneous from one scoring system to another, as well as predictive values.

5.6 Practical Section

5.6.1 Patients' Characteristics

Table 5.49 Patients' Characteristics

	N○	Age(mean)	Sex ratio(F/M)	Study design
All patients	12	53.42 ±14.41 (24-73)	1.2 (7/5)	Case Series

Patients' age range from 24 to 73 years with a female predominance.

5.6.2 Cancer Type

Table 5.50 Patients' Distribution according to their Cancer Type

Cancer Type	N○
Rectal cancer	2
Breast cancer	1
Gastric cancer	2
Ovarian and endometrial cancer	2
Colon cancer	3
Prostatic cancer	1
Lung Cancer	1
Total	12

Different cancer types are observed in the selected patients.

5.6.3 Laboratory Findings

5.6.4 Hematimetric Parameters

Table 5.51 Hematimetric Parameters of Selected Patients

Parameter	Control 1	Control 2
WBC(10^6mL^{-1})	5.73 ± 2,69	7.25 ± 5.16
HCT(%)	33.71 ± 3.47	31.93 ± 3.99
PLT(10^6mL^{-1})	200.83 ± 67.88	251.92 ± 184.87
ESR(mm)	50.4 ± 35.68	55.17 ± 37.87

WBC; white blood cells, HCT; hematocrite PLT; platelet count, ESR, erythrocyte sedimentation rate

White blood cells count and platelet count are in the normal range, but hematocrite and ESR are abnormal in the selected patients.

5.6.5 Hemostatic Parameters

Table 5.52 Global Coagulation Findings in the Selected Patients

Parameters	Control 1	Control 2
PT(s)	14.08 ± 2.72	14.8 ± 2.19
aPTT(s)	30.08 ± 3.18	35.61 ± 8.22
Fg($g\,dL^{-1}$)	2.56 ± 0.55	3.17 ± 0.90

PT; prothrombin time, aPTT; activated partial thromboplastin time, Fg; fibrinogen

PT values are slightly abnormal, but aPTT and Fg are in the normal range in both controls.

Table 5.53 Specific Markers Values in the Selected Patients

Parameters	Control 1	Control 2
FDP($\mu g\,mL^{-1}$)		
<10	91.7%	33.3%
>10 <25	8.3%	25%
>25	0	41.7%
AT(%)	115.14 ± 23.89	106.31 ± 32.23

FDP; fibrin degradation products, AT; antithrombin

Antithrombin levels are in the normal range in both controls. In the first control, almost all patients had levels of FDP less than $10\mu g\,mL^{-1}$. In the second one, the number of patients with levels of FDP more than $10\mu g\,mL^{-1}$ increased, and 41.7% had more than $25\mu g\,mL^{-1}$.

5.6.6 Distribution of Patients according to Abnormal Biological Parameters:

Table 5.54 Distribution of Patients according to Score Values

Score	Control 1	Control 2	Score 3
0	9	1	1
1	1	5	3
2	2	1	3
3	0	3	0
4	0	1	3
5	0	0	0
6	0	0	2

Score values slightly increased from control 1 to control 2 but all patients had a score <5 based on the laboratory findings of each control. The score increased when the evolution of the biological parameters were taken into account (score 3).

Table 5.55 Distribution of Patients according to the Abnormal Laboratory Findings

Parameter	Control 1	Control 2
PT	33.3%	58.3%
aPTT	58.3%	50%
Fg	8.3%	16.7%
PLT	16.7%	16.7%
WBC	25%	33.3%
HCT	66.6%	66.6%
ESR	66.6%	83.3%
AT	8.3%	16.6%
FDP	8.3%	83.3%

More patients had abnormal biological parameters in the second control.

Table 5.56 Distribution of Patients Based on the Presence or Absence of Non-overt DIC

	N∘ (Control 1)	N∘ (Control 2)	N ∘ (Score 3)
<5 (non-overt DIC -)	12	12	9
≥5 (non-overt DIC +)	0	0	3

Patients were diagnosed with non-overt DIC when the evolution of the biological parameters were taken into account.

5.6.7 Relation between Score Values and Biological Parameters

Table 5.57 Relation between Score 3 Values and Score Parameters

	Parameter	Score 3	Mean/(%)	P
Control 2	PT(s)	<5	13.92 ± 1.55	0.046
		≥5	17.43 ± 1.70	
	PLT(10^6mL^{-1})	<5	275.56 ± 210.33	0.224
		≥5	181 ± 31	
	Fg(g dL^{-1})	<5	3.4 ± 0.73	0.308
		≥5	2.48 ± 1.17	
	AT(%)	<5	106.19 ± 37.54	0.972
		≥5	106.67 ± 8.7	
	FDP(µg mL^{-1})			
	<10	<5	33.33%	0.61
		≥5	0	
	>10 <25	<5	25%	
		≥5	0	
		<5	16.66%	
	>25	≥5	25%	

PT; prothrombin time, aPTT, activated partial thromboplastin time, PLT; platelet count, Fg; fibrinogen, AT; antithrombin, FDP; Fibrin degradation products

There are no significant differences in score parameters between patients with score values of 5 and more and patients with less than 5 except for PT.

Correlation between Laboratory Findings in Control 2 and Score 3 Values

Table 5.58 Correlation between Score 3 Values and Laboratory Findings

Parameter	Pearson Correlation Coefficient (R)
PT	0.720**
aPTT	0.629*
PLT	-0.363
Fg	-0.606*
AT	-0.24

PT; prothrombin time, aPTT, activated partial thromboplastin time, PLT; platelet count, Fg; fibrinogen, AT; antithrombin, ∗0.05, ∗∗0.01

PT, aPTT are significantly and positively correlated with the observed score values. PLT and Fg are negatively and significantly correlated with the observed score values.

Table 5.59 Correlation between Score 3 Values and FDP Levels

Parameter	Spearman Correlation Coefficient
FDP	0.801**

FDP; fibrin degradation products

FDP levels are positively correlated with score values.

5.6.8 Relation between Complications and the Presence or Absence of Non-overt DIC

Table 5.60 Relation between Score 3 Values and Complications

Complication	Score	N○	P
Hemorrhage	<5	2	0.788
Thrombosis		1(8.33%)	
Infection		1(8.33%)	
Metastasis		2(16.66%)	
Hemorrhage	≥5	0	
Thrombosis		0	
Infection		0	
Metastasis		1(8.33%)	

The complications in the selected patients are not significantly related to higher score values.

5.6.9 Relation between Risk Factors and the Presence or Absence of Non-overt DIC

Table 5.61 Relation between Score 3 Values and Risk Factors

Risk Factor	Score	N○	P
Age		Mean 50±14.64	0.96
Surgery	<5	2(16.66%)	0.619
Aneurysm		1(8.33%)	
Diabetes		2(16.66%)	
HTA		4(33.33%)	
Surgery	≥5	0	
Aneurysm		0	
Age		M 63.67±8.62	
Diabetes		0	
HTA		1 (8.33%)	

The risk factors shown in the table are not significantly related to higher score values. The mean age in the group with a score ≥5 is higher than in the group with a score of <5 but not significantly.

Chapter 6

Discussion

Disseminated intravascular coagulation is an acquired pathology that is commonly associated with different diseases such as sepsis, malignancy and obstetric calamities (Bick 2003; Levi 2018); in addition to that, its frequency among these pathologies varies from one to another. We have noticed, in different studies, that the occurrence of DIC differs from one cancer to another as well; the higher frequencies are observed in APL and metastatic cancers (Bick 1992a; Agrawal et al. 2019). We have also found that some independent factors may influence the occurrence of DIC like age, gender, cancer stage, complication of cancer by metastasis and the histological characteristics of tumor; for example, carcinomas are often associated with DIC according to Aota et al. 2016).

In our series of cases study, we found an average age of 53.42 years. It corresponds to the average age found in Mirka's study (Sivula et al. 2005), but it is older than that of Sawamura et al. 2009 study (45 years) and younger than that of Del Carpio-Orantes and García-Ortiz 2014; Koami et al. 2017; Zhang et al. 2017 (60.36 - 71 years respectively). Also, there was more female patients than male ones in our study. The presence of risk factors that may be associated with DIC according to different studies (Sallah et al. 2001, Wada et al. 2010...) was not significantly associated with non-overt DIC in our study; this may be due to the small population size. We also found that diabetes and hypertension were the most frequently found co-morbidities in the selected patients, and this has been reported in Del Carpio-Orantes and García-Ortiz 2014 study. Concerning the age, we found that it was higher in the non-overt DIC (+) group than in the non-overt DIC (-) one, but it was not significant. Many tests are available today for the diagnosis of DIC, both in a routine setting or in a more specialized or research laboratory. But most of these tests are not sufficient to diagnose DIC with adequate certainty. Indeed, there is no single laboratory test that has an adequate sensitivity and specificity on itself to confirm or reject a diagnosis of DIC. Some studies showed that prothrombin time was prolonged in about 50 to 75% of patients with DIC (Bick 1996), and it was normal or short in about 50% of patients. PT, as well as aPTT, is generally unreliable and of minimal usefulness in evaluating DIC. Concerning FDPs, they are only indicative of the presence of plasmin, so it can be found elevated in other clinical situations (Bick 1996). Platelet count is generally normal in chronic DIC; this is due to compensatory hyperproduction of platelet, or apparently normal during DIC combined with an inflammatory state (Dumas et al. 2012). For this reason, the combination of several readily available coagulation tests may be helpful to establish this diagnosis. This was confirmed when we found that GCT score had a high AUC and specificity, but the sensitivity for a cutoff value of 4 points was low, and the addition of reduced platelet count (RPC), AT, and SF/TAT, increased the AUC for a cutoff value of 6 points. This suggests that the combination of hemostatic molecular markers levels and GCT was able to increase the sensitivity and specificity for the diagnosis of DIC (Aota et al. 2016). Concerning hematological malignancies, the absence of platelet count in GCT did not affect their sensitivity or specificity, but it displayed a high sensitivity even when platelet count were not taken into consideration, which suggests that GCT are useful supportive tools for the diagnosis of DIC in hematological cancer. In order to overstep these limitations, the SSC of ISTH recommended the use of scoring systems in 2001, and many have been and are still developed.

Ideally, every pathology would have its own score, but the feasibility of this is impossible in the field. This is why these systems are either used for the diagnosis of patients with any underlying condition, or are divided into two templates; one for hematopoietic injuries and

another for non-hematopoietic injuries. Several studies have compared the ISTH score with Japanese scores (Gando et al. 2016; Wada et al. 2003b; Investigations 2006). In 2005, in a study of patients with thrombocytopenia, 33.3%, 42.3%, and 64.7% were diagnosed with DIC according to ISTH, JMHW, and JAAM respectively (Gando and Otomo 2015). Similar results were reported in a multicenter prospective study conducted in 2006 on a series of 273 patients, suggesting that JAAM was the most sensitive of the three scores; in a retrospective cohort study of 314 trauma patients, Sawamura and colleagues found that the JAAM score was capable of diagnosing all patients who developed DIC that had a score of less than 5 based on the ISTH criteria (Sugawara et al. 2013). ISTH and JMWH criteria have a low sensitivity to DIC in patients with sepsis, as patients with sepsis have low levels of PDF and high levels of fibrinogen compared to patients with leukemia. Overall, the ISTH and JAAM scores show no fundamental difference, which is not surprising since they are all based on the same parameters. However, there is a greater simplicity of use for the ISTH score. The lack of sensitivity of the latter is partially corrected when the test is repeated daily, which is imperative in the case of a situation with a risk of developing DIC (Lerolle et al. 2008). The concordance rate in the diagnosis of DIC between ISTH and JMHW differs depending on the underlying diseases responsible for causing DIC. It is slightly higher in patients with trauma or acute promyelocytic leukemia. In 2003, Wada et al. compared the two scores and showed that the concordance rate in the diagnosis of overt DIC, according to the ISTH and JMHW criteria, was 67.4% , while Luo et al compared between CDSS, ISTH and JMHW and found a concordance rate of 81.7% ,84.7% between the CDSS, ISTH and CDSS, JMHW respectively in non-hematological disorders and 80%, 76.90% between the CDSS, ISTH and CDSS, JMHW in hematological disorders (Luo et al. 2019).

DIC is commonly related to "death is coming", because the appearance of a decompensated state is often associated with a poor outcome. For this reason, clinicians found it necessary to diagnose DIC at an early stage, which is called non-overt DIC or pre-DIC stage. Kaneko and Wada 2011 mentioned that the initiation of treatment in the pre-DIC state was associated with a remission in 80% of cases. In addition to previous scores, new ones are still proposed for the diagnosis of non-overt DIC; either by modifying cutoff values and exploring dynamic changes of different markers, or by testing new markers that may be more relevant for detecting mild coagulation abnormalities. We found in the literature, studies that evaluated modified versions of already known scores. Lee and Song found the same death rate in non-DIC and non-overt DIC patients according to non-overt ISTH and the modified ISTH (Lee and Song 2010). Also, Toh and Downey 2005 evaluated the non-overt scoring system proposed by the SSC of the ISTH and found an acceptable specificity for death, but with a low sensitivity.

In our study, the diagnosis of DIC was carried out using the modified diagnostic criteria for non-overt disseminated intravascular coagulation proposed by Wada et al. 2012. In the 25% of patients that were diagnosed with non-overt DIC using the modified diagnostic criteria (Wada et al. 2012), FDP and PT were the most abnormal parameters, which is in line with the data in the literature. It was found that 85-100% of the confirmed DIC cases had an elevation of FDP's levels (Bick 1992b), and the mean value of PT was 15s according to our results, which corresponds to the results reported by Del Carpio-Orantes and García-Ortiz 2014 (15s, 25s). Also, we observed: first, a significant positive correlation between prothrombin time, activated partial thromboplastin time, FDP and the values of score 3, and second, a significant negative correlation between score 3 values and fibrinogen level.

Today, new diagnostic trails are evaluated, like Thromboelastography (TEG) that is a whole blood coagulation assay in which a small sample of blood is rotated in a cuvette, and in which the strength, elasticity, and dissolution of the forming clot are measured by a torsion wire or by optical means.

A variation to this test is rotational thromboelastometry (ROTEM) in which a spinning pin is positioned in a cuvette with a whole blood sample where clotting is detected by reduced rotation of the pin. DIC as measured with thromboelastography was demonstrated to have a good correlation with clinically important organ dysfunction and survival; although, its superiority over more common coagulation tests has not yet been established. In a systematic review of 2 randomized controlled trials and 16 observational studies in sepsis, thromboelastography was shown to correctly identify relevant coagulation changes. There

was also a relationship between abnormalities in thromboelastography (in particular parameters reflecting speed of clot formation and clot strength) and reduced survival. The use of thromboelastography for the diagnosis of DIC has not been systematically studied, although some authors believe that the test may be useful for appraising coagulopathies in critically ill patients. Another test to assess hypercoagulability in critically ill patients is the activated partial thromboplastin (aPTT) biphasic waveform analysis that can be detected on some optical coagulation analyzers. The biphasic waveform is related to the appearance of complexes of very low density lipoprotein and C-reactive protein, and their presence was shown to have more than 90% accuracy (Levi 2018).

Chapter 7

Conclusion

We found through previous studies that cancer, as well as other pathologies, is associated with coagulopathies that are likely to worsen the prognosis. One of them is Disseminated Intravascular Coagulation which is a devastating syndrome characterized by a systemic activation of coagulation cascade, which may result in severe bleeding (that may induce hypothermia, hypotension and tissue necrosis Dumas et al. 2006), as well as thrombotic problems that may lead to multiple organ failure. The factors that may be related to the occurrence of DIC in cancer patients are gender, age and the presence of necrosis in tumor cells Sallah et al. 2001. Early diagnosis and accurate prognosis are important in improving DIC patients' outcome. At first times, diagnosis of DIC relied on global coagulation test like platelet counts, PT, aPPT, measurement of fibrinogen. But their usefulness in evaluating DIC were soon limited; this is why new diagnostic criteria were developed, using hemostatic markers like factor VIII, factor II, factor V, TAT, SF, prothrombin fragments 1+2 (F1+2), plasmin–plasmin inihibitor complex (PPIC) and D-dimer tests. Indeed, it was found that they are more helpful than global coagulation tests, and seem to be more relevant for the diagnosis of DIC. However, a disadvantage of these tests is that their use does not suit emergency situations, and it is limited to specialized laboratories. Thus, combinations of several readily available coagulation tests may be helpful to establish DIC diagnosis. Therefore, the diagnostic scoring systems for DIC use a combination of these laboratory tests in the form of a template that is inexpensive and readily available. Also, scores show a high sensitivity and specificity as regards the establishment or ruling out a diagnosis of DIC. It is important to notice that scoring systems have failed in discriminating between survivors and non survivors among DIC patients. In the last few years, new diagnostic trails were and are still evaluated, such as Thromboelastography (TEG), and its variation rotational Thromboelastometry (ROTEM). The activated partial thromboplastin (aPTT) biphasic waveform analysis, which corrected some limits of scoring systems, seems to have a good correlation with clinically important organ dysfunction and survival.

In the absence of a gold standard for the diagnosis of DIC, the best tests should be chosen depending on their availability, sensitivity and specificity, and their usefulness in an emergency situation.

Appendix A

Appendices

A.1 Appendice A

Table A.1 Modified diagnostic criteria for DIC established by the Japanese Ministry of Health and Welfare

	With hematopoietic disorders	Without hematopoietic disorders
Underlying disease	1 point	1 point
Clinical symptoms	bleeding 0point organ failure 1point	bleeding 1 point organ failure 1 point
Platelet count($10^3\mu L^{-1}$)	0 point	>80 but <120; 1point, >50 but<80; 2points, <50; 3points
Fibrin-related marker	FDP($\mu g\,mL^{-1}$)> 10 but <20; 1point, >20 but <40; 2point; >40; 3point	FDP($\mu g\,mL^{-1}$)> 10 but <20; 1point, >20 but <40; 2point; >40; 3point
Fibrinogen($g\,L^{-1}$)	>1 but <1.5; 1point, <1; 2point	>1 but <1.5; 1point, <1; 2point
PT (PT ratio)	>1.25 but <1.67; 1point, >1.67; 2point	>1.25 but <1.67; 1point, >1.67; 2point
Diagnosis of DIC	≥4point	≥7point

A.2 Appendix B

Table A.2 Modified Diagnostic Criteria for non-overt DIC proposed by Wada et al. 2012

Laboratory test	Present data	Points		Change in data	Point		Score
Platelet counts ($\times 10^9 L^{-1}$)	>100	0	+	>50% reduction	1	=	
	50–100	1	+	>50% reduction	1	=	A
	<50	2	+		0	=	
FDP ($mg\,L^{-1}$)	<10	0	+	Five fold increase	1	=	
	10–25	1	+	Five fold increase	1	=	B
	>25	2	+		0	=	
Fibrinogen ($g\,L^{-1}$)	>1.0	0	+	>50% reduction	1	=	
	0.5–1.0	1	+	>50% reduction	1	=	C
	<0.5	2	+		0	=	
PT(s)	<14.0	0	+	Prolongation: >2.0	1	=	
	14.0–17.0	1	+	Prolongation: >2.0	1	=	D
	>17.0	2	+		0	=	
AT	<70%	1				=	E
FMC >10 $mg\,L^{-1}$ or TAT >10 $\mu g\,L^{-1}$						=	F
Diagnosis of DIC and pre-DIC: A+B+C+D+E+F *geq*5							

Technical Data Form

Date	
N°	
Date of last sampling	

Patient's ID

Institution		Departement
Last name		First name
Gender	Male ☐ Female ☐	Age
Adress		

Clinical Data

Pathology
Date of Diagnosis
medical-surgical background
Family background
Personal background
Antimitotic treatement

Complications

t

Figure A.1: Technical Data Form (page1)

A.3 Appendix C

Bilogical Parameters

Date:

PLT:

PT:

aPTT:

Fg:

AT:

FDP:

ESR:

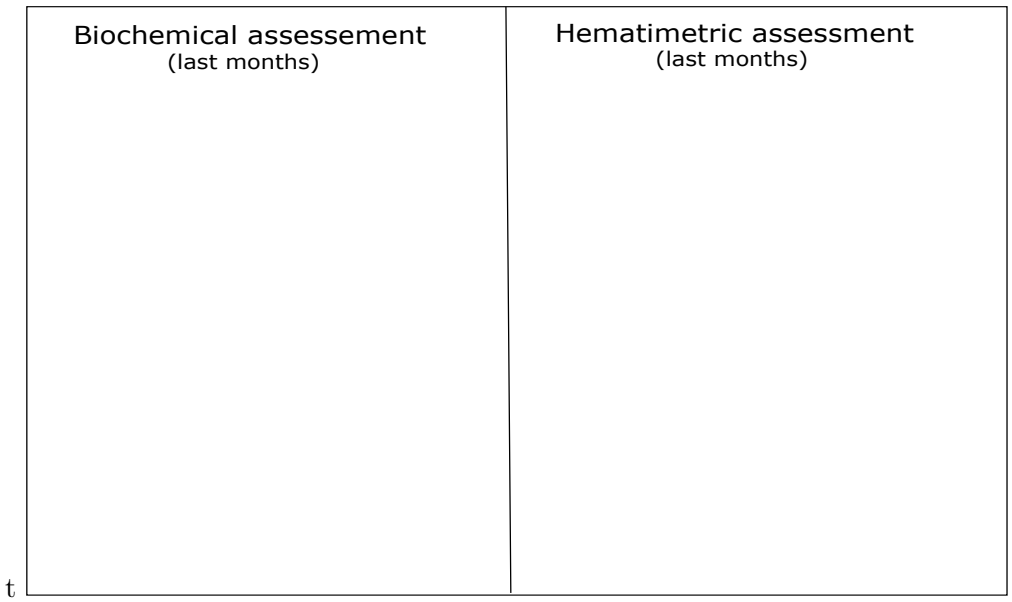

Figure A.2: Technical Data Form (page2)

Bibliography

[1] Kavita Agrawal, Nirav Agrawal, and Levin Miles. "Disseminated Intravascular Coagulation as an Initial Manifestation of Metastatic Prostate Cancer Emergently Treated with Docetaxel-Based Chemotherapy". In: *Case Reports in Oncological Medicine* 2019 (2019), pp. 1–6. ISSN: 2090-6706. DOI: 10.1155/2019/6092156.

[2] MD Akhilesh Kumar Tiwari, MD1* , Michell Gulabani, MD2, Prashant Dass, MD3 and Rishi Raj Sanjay. *disseminated intavascular coagulation*. Ed. by MD (Editor) Balwinder Singh. 2013, p. 202. ISBN: 6312317269.

[3] Takumi Aota et al. "Evaluation of the Diagnostic Criteria for the Basic Type of DIC Established by the Japanese Society of Thrombosis and Hemostasis". In: *Clinical and Applied Thrombosis/Hemostasis* 23.7 (2016), pp. 838–843. ISSN: 19382723. DOI: 10.1177/1076029616672582.

[4] Review Article. "Disseminated intravascular coagulation". In: 58.5 (2014). DOI: 10.4103/0019-5049.144666.

[5] Hidesaku Asakura. *Classifying types of disseminated intravascular coagulation: Clinical and animal models*. 2014. DOI: 10.1186/2052-0492-2-20.

[6] Hidesaku Asakura et al. "An enhanced fibrinolysis prevents the development of multiple organ failure in disseminated intravascular coagulation in spite of much activation of blood coagulation". In: *Critical Care Medicine* 29.6 (2001), pp. 1164–1168. ISSN: 00903493. DOI: 10.1097/00003246-200106000-00015.

[7] Hidesaku Asakura et al. "Proposal for new diagnostic criteria for DIC from the Japanese Society on Thrombosis and Hemostasis". In: *Thrombosis Journal* 14.1 (2016), pp. 1–13. ISSN: 14779560. DOI: 10.1186/s12959-016-0117-x. URL: http://dx.doi.org/10.1186/s12959-016-0117-x.

[8] MD (Editor) Balwinder Singh. *Disseminated Intravascular Coagulation (DIC): Clinical Manifestations, Diagnosis and Treatment Options*. 2014.

[9] R. L. Bick. "Coagulation abnormalities in malignancy: A review". In: *Seminars in Thrombosis and Hemostasis* 18.4 (1992), pp. 353–372. ISSN: 00946176. DOI: 10.1055/s-2007-1002575.

[10] R. L. Bick. "Coagulation abnormalities in malignancy: A review". In: *Seminars in Thrombosis and Hemostasis* 18.4 (1992), pp. 353–372. ISSN: 00946176. DOI: 10.1055/s-2007-1002575.

[11] Rodger L Bick. "Disseminated intravascular coagulation Current concepts of etiology , pathophysiology , diagnosis , and treatment". In: 17 (2003), pp. 149–176.

[12] Rodger L. Bick. "Disseminated intravascular coagulation: Objective clinical and laboratory diagnosis, treatment, and assessment of therapeutic response". In: *Seminars in Thrombosis and Hemostasis* 22.1 (1996), pp. 69–88. ISSN: 00946176. DOI: 10.1055/s-2007-998993.

[13] Émilie Buache and Marie Christine Rio. "The tumoral stroma, a breeding ground for cancer cells". In: *Medecine/Sciences* 30.4 (2014), pp. 385–390. ISSN: 1958-5381. DOI: 10.1051/medsci/20143004011.

[14] *CM1*. URL: http://en.wikipedia.org/wiki/Image:Purpura.jpg.

[15] *CM2*. URL: http://en.wikipedia.org/wiki/Image:Purpura.jpg.

[16] Associated Clinical Conditions. "Tion in Patients With Infections Are Cell-Specific Mem- Brane Components of the Microorganism, Such As Lipopolysaccharide or Endotoxin, or Bacterial Exo- Toxins (E.G., Staphylococcal". In: *Vascular Medicine* (1999).

[17] Luis Del Carpio-Orantes and Jorge José García-Ortiz. "Disseminated intravascular coagulation. Case series and literature review". In: *Revista medica del Instituto Mexicano del Seguro Social* 52.6 (2014), pp. 680–683. ISSN: 04435117.

[18] J. F. Dhainaut and J. Charpentier. "CIVD et défaillance d'organes: Arguments expérimentaux et cliniques". In: *Reanimation* 11.8 (2002), pp. 599–607. ISSN: 16240693. DOI: 10.1016/S1624-0693(02)00307-9.

[19] Yaren Dirik and Pınar Kolusarı. "Modality for disseminated intravascular coagulation and current treatment". In: *Eastern Journal of Medicine* 24.3 (2019), pp. 393–400. ISSN: 13010883. DOI: 10.5505/ejm.2019.24085.

[20] Ashish Dixit et al. "Disseminated intravascular coagulation in acute leukemia at presentation and during induction therapy". In: *Clinical and Applied Thrombosis/Hemostasis* 13.3 (2007), pp. 292–298. ISSN: 10760296. DOI: 10.1177/1076029607302435.

[21] Kenneth Byrd Do. *DISSEMINATED INTRAVASCULAR*. Elsevier, 2020, pp. 406–408. DOI: 10.1016/B978-0-323-71184-5.00086-0. URL: http://dx.doi.org/10.1016/B978-0-323-71184-5.00086-0.

[22] Geneviève Du Pont-Thibodeau, Jean Sébastien Joyal, and Jacques Lacroix. "Management of neonatal sepsis in term newborns". In: *F1000Prime Reports* 6.June 2015 (2014). ISSN: 20517599. DOI: 10.12703/P6-67.

[23] Guillaume Dumas et al. "Coagulation intravasculaire disséminée". In: 62.5 (2006), p. 604. ISSN: 00352640. DOI: 10.1016/s1155-1984(06)40045-5.

[24] Guillaume Dumas et al. "Coagulation intravasculaire disséminée". In: *Revue du Praticien* 62.5 (2012), p. 604. ISSN: 00352640. DOI: 10.1016/s1155-1984(06)40045-5. URL: http://dx.doi.org/10.1016/S1155-1984(06)40045-5.

[25] John Libbey Eurotext et al. "Synthèse Coagulation intravasculaire disséminée et tumeurs solides Disseminated intravascular coagulation in solid tumours". In: 101 (2020), pp. 580–592. DOI: 10.1684/bdc.2014.1959.

[26] Fast Facts. "How I Treat In Brief : Managing Disseminated Intravascular Coagulation". In: (2020), pp. 1–7.

[27] Donald I Feinstein. "Treatment of Disseminated Intravascular Coagulation". In: 14.4 (1988).

[28] *Fibrinolysis*. URL: http://oer2go.org/mods/en-boundless/www.boundless.com/physiology/textbooks/boundless-anatomy-and-physiology-textbook/cardiovascular-system-blood-17/hemostasis-168/fibrinolysis-842-1162/index.html.

[29] Massimo Franchini et al. "Disseminated Intravascular Coagulation in Hematologic Malignancies". In: (2010).

[30] S Gando. "The Utility of a Diagnostic Scoring System for Disseminated Intravascular Coagulation". In: *CCC* 28.3 (2012), pp. 373–388. ISSN: 0749-0704. DOI: 10.1016/j.ccc.2012.04.004. URL: http://dx.doi.org/10.1016/j.ccc.2012.04.004.

[31] Satoshi Gando, Marcel Levi, and Cheng Hock Toh. "Disseminated intravascular coagulation". In: *Nature Reviews Disease Primers* 2.Dic (2016), pp. 1–16. ISSN: 2056676X. DOI: 10.1038/nrdp.2016.37. URL: http://dx.doi.org/10.1038/nrdp.2016.37.

[32] Satoshi Gando and Yasuhiro Otomo. "systemic disseminated intravascular coagulation in trauma and traumatic shock". In: (2015), pp. 1–11. DOI: 10.1186/s13054-015-0735-x.

[33] Bezeaud M C Guillin. "Physiologie de la coagulation". In: (2001), pp. 13–19.

[34] Stephen R Hanson and Erik I Tucker. *CHAPTER II . 2 . 6 BLOOD COAGULATION AND BLOOD – MATERIALS INTERACTIONS*. Third Edit. 1997. Elsevier, 2007, pp. 551–557. DOI: 10.1016/B978-0-08-087780-8.00048-6.

[35] Mhamed Harif. "Hemostase". In: September (2015).

[36] Mineji Hayakawa, Satoshi Gando, and Hirokatsu Hoshino. "A Prospective Comparative Study of Three Sets of Criteria for Disseminated Intravascular Coagulation : ISTH Criteria vs Japanese Criteria". In: 8 (2007), pp. 65–72. DOI: 10.1177/1076029606296405.

[37] editors Holzheimer RG, Mannick JA. *Surgical Treatment: Evidence-Based and Problem-Oriented*. Munich, 2001.

[38] Clinical Investigations. "A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: Comparing current criteria*". In: 34.3 (2006), pp. 625–631. DOI: 10.1097/01.CCM.0000202209.42491.38.

[39] Eefje Jong et al. *The Crosstalk of Inflammation and Coagulation in Infectious Disease and Their Roles in Disseminated Intravascular Coagulation*. Fourth Edi. Elsevier Inc., 2013, pp. 190–201. ISBN: 9781455722969. DOI: 10.1016/B978-1-4557-2296-9.00013-0. URL: https://doi.org/10.1016/B978-0-323-46202-0.00013-3.

[40] De Jonge. "ChapterChapter 2 Currentt Drug Treatment Strategies for Disseminatedd Intravascular Coagulation". In: (2020).

[41] Toshihiro Kaneko and Hideo Wada. "Diagnostic Criteria and Laboratory Tests for Disseminated Intravascular Coagulation". In: *Journal of Clinical and Experimental Hematopathology* 51.2 (2011), pp. 67–76. DOI: 10.3960/jslrt.51.67.

[42] Margaret Karpatkin. "Diagnosis and Management of Coagulation". In: *Laboratory Diagnosis* 18.1 (1971), pp. 23–38. ISSN: 0031-3955. DOI: 10.1016/S0031-3955(16)32520-2. URL: http://dx.doi.org/10.1016/S0031-3955(16)32520-2.

[43] David A Bender Kathleen M Botham, Anthony Weil, Victor W Rodwell, Peter J Kennelly. *Biochimie de Harper*. 6 eme. 2017, p. 840. URL: https://books.google.dz/books?id=2CM2DwAAQBAJ{\&}printsec=frontcover{\&}dq=biochimie+harper{\&}hl=en{\&}sa=X{\&}ved=2ahUKEwj1rJWl7ZjrAhVTThUIHVykA-MQ6AEwAHoECAUQAg{\#}v=onepage{\&}q=biochimieharper{\&}f=false.

[44] Kazuo Kawasugi et al. "Prospective evaluation of hemostatic abnormalities in overt DIC due to various underlying diseases". In: *Thrombosis Research* 128.2 (2011), pp. 186–190. ISSN: 00493848. DOI: 10.1016/j.thromres.2011.02.015. URL: http://dx.doi.org/10.1016/j.thromres.2011.02.015.

[45] H. Koami et al. "What factor within the Japanese Association for Acute Medicine (JAAM) disseminated intravascular coagulation (DIC) criteria is most strongly correlated with trauma induced DIC? A retrospective study using thromboelastometry in a single center in Japan". In: *European Journal of Trauma and Emergency Surgery* 43.4 (2017), pp. 431–438. ISSN: 16153146. DOI: 10.1007/s00068-016-0756-4.

[46] J. Kramer et al. "The association of disseminated intravascular coagulation with specific diseases". In: *Reanimation* 11.8 (2002), pp. 575–583. ISSN: 16240693. DOI: 10.1016/S1624-0693(02)00301-8.

[47] Shigeki Kushimoto et al. "Increased ratio of soluble fibrin formation/thrombin generation in patients with DIC". In: *Clinical and Applied Thrombosis/Hemostasis* 18.6 (2012), pp. 628–632. ISSN: 10760296. DOI: 10.1177/1076029612451648.

[48] Dominique Lasne, Brigitte Jude, and Sophie Susen. "From normal to pathological hemostasis". In: *Canadian Journal of Anesthesia* 53.2 (2006), pp. 2–11. ISSN: 0832610X. DOI: 10.1007/bf03022247.

[49] Jong Hwa Lee and Jaewoo Song. "Diagnosis of non-overt disseminated intravascular coagulation made according to the International Society on Thrombosis and Hemostasis criteria with some modifications". In: *The Korean Journal of Hematology* 45.4 (2010), p. 260. ISSN: 1738-7949. DOI: 10.5045/kjh.2010.45.4.260.

[50] N Lerolle, D Borgel, and J Diehl. "Approche critique des critères diagnostiques de coagulation intravasculaire disséminée Appraisal of the diagnostic criteria for disseminated intravascular coagulation". In: (2008), pp. 348–354. DOI: 10.1016/j.reaurg.2008.03.014.

[51] M Levi. "Pathogenesis and diagnosis of disseminated intravascular coagulation". In: 40.February (2018), pp. 15–20. DOI: 10.1111/ijlh.12830.

[52] M. Levi et al. "Guidelines for the diagnosis and management of disseminated intravascular coagulation". In: *British Journal of Haematology* 145.1 (2009), pp. 24–33. ISSN: 00071048. DOI: 10.1111/j.1365-2141.2009.07600.x.

[53] Marcel Levi. "Cancer-related coagulopathies". In: *Thrombosis Research* 133.SUPPL. 2 (2014), S70–S75. ISSN: 18792472. DOI: 10.1016/S0049-3848(14)50012-6. URL: http://dx.doi.org/10.1016/S0049-3848(14)50012-6.

[54] Marcel Levi. "Disseminated intravascular coagulation". In: *Critical Care Medicine* 35.9 (2007), pp. 2191–2195. ISSN: 00903493. DOI: 10.1097/01.CCM.0000281468.94108.4B.

[55] Marcel Levi. "Disseminated intravascular coagulation". In: *Critical Care Medicine* 35.9 (2007), pp. 2191–2195. ISSN: 00903493. DOI: 10.1097/01.CCM.0000281468.94108.4B.

[56] Marcel Levi. "Disseminated intravascular coagulation in cancer patients". In: *Best Practice and Research: Clinical Haematology* 22.1 (2009), pp. 129–136. ISSN: 15216926. DOI: 10.1016/j.beha.2008.12.005. URL: http://dx.doi.org/10.1016/j.beha.2008.12.005.

[57] Marcel Levi, Evert De Jonge, and Tom Van Der Poll. "New treatment strategies for disseminated intravascular coagulation based on current understanding of the pathophysiology". In: 2 (2004), pp. 41–49. DOI: 10.1080/07853890310017251.

[58] Marcel Levi and Joost C. Meijers. "DIC: Which laboratory tests are most useful". In: *Blood Reviews* 25.1 (2011), pp. 33–37. ISSN: 0268960X. DOI: 10.1016/j.blre.2010.09.002. URL: http://dx.doi.org/10.1016/j.blre.2010.09.002.

[59] Giuseppe Lippi. "of disseminated intravascular coagulation". In: March 2014 (2006). DOI: 10.1186/1477-9560-4-4.

[60] Giuseppe Lippi and Gianfranco Cervellin. "Disseminated Intravascular Coagulation in Trauma Injuries". In: ().

[61] Lili Luo et al. "A multicenter, prospective evaluation of the Chinese Society of Thrombosis and Hemostasis Scoring System for disseminated intravascular coagulation". In: *Thrombosis Research* 173 (2019), pp. 131–140. ISSN: 18792472. DOI: 10.1016/j.thromres.2018.11.022.

[62] T. Matsuda. "Clinical aspects of DIC - Disseminated intravascular coagulation". In: *Polish Journal of Pharmacology*. 1996.

[63] Jan Hawthorne Maxson. "Management of Disseminated lntravascular Coagulation". In: *Critical Care Nursing Clinics of North America* 12.3 (2000), pp. 341–352. ISSN: 0899-5885. DOI: 10.1016/S0899-5885(18)30099-6. URL: https://doi.org/10.1016/S0899-5885(18)30099-6.

[64] Heng Mei et al. "Evaluation the combined diagnostic value of TAT, PIC, tPAIC, and sTM in disseminated intravascular coagulation: A multi-center prospective observational study". In: *Thrombosis Research* 173.November 2018 (2019), pp. 20–26. ISSN: 18792472. DOI: 10.1016/j.thromres.2018.11.010.

[65] NIC. *Plasma Cell Neoplasms (Including Multiple Myeloma) Treatment (PDQ®)–Patient Version*. 2020.

[66] C. Nougier and A. Marijon. "Caractéristiques immuno-analytiques des D-dimères". In: *Immuno-Analyse et Biologie Specialisee* 27.2 (2012), pp. 83–88. ISSN: 09232532. DOI: 10.1016/j.immbio.2012.01.006. URL: http://dx.doi.org/10.1016/j.immbio.2012.01.006.

[67] Kenji Okajima, Yumi Sakamoto, and Mitsuhiro Uchiba. "Heterogeneity in the incidence and clinical manifestations of disseminated intravascular coagulation: A study of 204 cases". In: *American Journal of Hematology* 65.3 (2000), pp. 215–222. DOI: 10.1002/1096-8652(200011)65:3<215::AID-AJH7>3.0.CO;2-7. eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1002/1096-8652%28200011%2965%3A3%3C215%3A%3AAID-AJH7%3E3.0.CO%3B2-7. URL: https://onlinelibrary.wiley.com/doi/abs/10.1002/1096-8652%28200011%2965%3A3%3C215%3A%3AAID-AJH7%3E3.0.CO%3B2-7.

[68] Kohji Okamoto et al. "Frequency and hemostatic abnormalities in pre-DIC patients". In: *Thrombosis Research* 126.1 (2010), pp. 74 –78. ISSN: 0049-3848. DOI: https://doi.org/10.1016/j.thromres.2010.03.017. URL: http://www.sciencedirect.com/science/article/pii/S0049384810002069.

[69] E Pasquini et al. "Acute disseminated intravascular coagulation syndrome in cancer patients". In: *Oncology* (1995). DOI: 10.1159/000227520.

[70] Mercy Halleluyah Periayah et al. "Mechanism Action of Platelets and Crucial Blood Coagulation Pathways in Hemostasis". In: 11.4 (2017).

[71] Jacques Pélissie Philippe Codine, Nelly Kotzki. *COAGULATION, THROMBOSE ET MÉDECINE PHYSIQUE*. Ed. by Masson. 2005, p. 128. URL: https://books.google.dz/books?id=rk6vUP1{_}ER8C{\&}printsec=frontcover{\&}dq=coagulation+thrombose+et+medecine+physique{\&}hl=en{\&}sa=X{\&}ved=2ahUKEwiJtcm08JjrAhW3VRUIHWkFBvMQ6AEwAHoECAMQAg{\#}v=onepage{\&}q=coagulationthromboseetmedecinephysique{\&}f=false.

[72] Chest Physicians. "The systemic inflammatory response syndrome :" in: (1998), pp. 1–7.

[73] J. L. (Eds.) Porter, R. S., & Kaplan. *NoThe Merck manual of diagnosis and therapy.The Merck manual of diagnosis and therapy (19th ed.) Title*. Ed. by Merck Sharp & Dohme Corp. 2011.

[74] Raffaella Priora. "Platelet function tests : a comparative review". In: (2015), pp. 133–148.

[75] T De Revel Professeur and K Doghmi Assistant. "Physiologie de l ' hémostase The Normal Haemostatic Process". In: 1 (2004), pp. 71–81. DOI: 10.1016/S1762-5661(03)00007-2.

[76] Majed Refaai. "LabMed Hemostasis Defects Associated with Liver Disease What Tests Should I Request to Confirm My Clinical Dx ? In addition , what follow-up tests might be useful ?" In: (2020), pp. 1–7.

[77] T de Revel and K Doghmi. "Physiologie de l ' hémostase The Normal Haemostatic Process". In: *EMC-dentisterie* 1 (2004), pp. 71–81. DOI: 10.1016/S1762-5661(03)00007-2.

[78] Henry M. Rinder Robert S. Hillman, Kenneth A. Ault, Michel Leporrier. *Hematology in Clinical Practice, 5e*. 2011.

[79] Alain Ruffion et al. "Successful use of samarium 153 for emergency treatment of disseminated intravascular coagulation due to metastatic hormone refractory prostate cancer". In: *Journal of Urology* (2000). ISSN: 00225347. DOI: 10.1016/S0022-5347(05)67308-9.

[80] S. Sallah et al. "Disseminated intravascular coagulation in solid tumors: Clinical and pathologic study". In: *Thrombosis and Haemostasis* 86.3 (2001), pp. 828–833. ISSN: 03406245. DOI: 10.1055/s-0037-1616139.

[81] Atsushi Sawamura et al. "Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality". In: *Thrombosis Research* 124.5 (2009), pp. 608–613. ISSN: 00493848. DOI: 10.1016/j.thromres.2009.06.034. URL: http://dx.doi.org/10.1016/j.thromres.2009.06.034.

[82] Mirka Sivula, Minna Tallgren, and Ville Pettilä. "Modified score for disseminated intravascular coagulation in the critically ill". In: *Intensive Care Medicine* 31.9 (2005), pp. 1209–1214. ISSN: 03424642. DOI: 10.1007/s00134-005-2685-2.

[83] K. E. Sletnes, H. C. Godal, and F. Wisløff. "Disseminated intravascular coagulation (DIC) in adult patients with acute leukaemia". In: *European Journal of Haematology* 54.1 (1995), pp. 34–38. ISSN: 16000609. DOI: 10.1111/j.1600-0609.1995.tb01623.x.

[84] Sumit Sohal et al. "Case Report Disseminated Intravascular Coagulation and Malignancy : A Case Report and Literature Review". In: 2020 (2020).

[85] Alessandro Squizzato and Hideo Wada. "Supportive management strategies for disseminated intravascular coagulation An international consensus". In: December (2015). DOI: 10.1160/TH15-09-0740.

[86] Junichi Sugawara et al. "Efficacy of recombinant human soluble thrombomodulin in severe postpartum hemorrhage with disseminated intravascular coagulation". In: *Clinical and Applied Thrombosis/Hemostasis* 19.5 (2013), pp. 557–561. ISSN: 10760296. DOI: 10.1177/1076029612443305.

[87] Tetsushi Takemitsu et al. "Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation". In: *Thrombosis and Haemostasis* 105.1 (2010), pp. 40–44. ISSN: 03406245. DOI: 10.1160/TH10-05-0293.

[88] Tetsushi Takemitsu et al. "Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation". In: *Thrombosis and Haemostasis* 105.1 (2011), pp. 40–44. ISSN: 03406245. DOI: 10.1160/TH10-05-0293.

[89] Jr Taylor et al. *Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation: On behalf of the scientific subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and*. 2001. DOI: 10.1055/s-0037-1616068.

[90] Jecko Thachil. "Expert Review of Hematology Disseminated intravascular coagulation – new pathophysiological concepts and impact on management". In: 4086.June (2016). DOI: 10.1080/17474086.2016.1203250.

[91] Jecko Thachil and Cheng-hock Toh. "Blood Reviews Disseminated intravascular coagulation in obstetric disorders and its acute haematological management". In: *Blood Reviews* 23.4 (2009), pp. 167–176. ISSN: 0268-960X. DOI: 10.1016/j.blre.2009.04.002. URL: http://dx.doi.org/10.1016/j.blre.2009.04.002.

[92] * Thomas N. Seyfried1 and Leanne C. Huysentruyt. *On the Origin of Cancer Metastasis*. 2013. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597235/.

[93] Anna Falanga Tiziano Barbui. "Disseminated intravascular coagulation in acute leukemia". In: *Acta Haematologica Polonica* 46.2 (2001), pp. 128–132. ISSN: 00015814. DOI: 10.1016/j.achaem.2015.02.014.

[94] CH Toh and C Downey. "Performance and prognostic importance of a new clinical and laboratory scoring system for identifying non-overt disseminated intravascular coagulation". In: *Blood Coagul Fibrinolysis* (2005). DOI: 10.1097/00001721-200501000-00011.

[95] Cheng-hock Toh et al. "Current Pathological and Laboratory Considerations in the Diagnosis of Disseminated Intravascular Coagulation". In: Dic (2016), pp. 505–512.

[96] Jan Urge and Jan Strojil. "EARLY DIAGNOSIS OF DIC DEVELOPMENT INTO THE OVERT PHASE Jan Urge". In: 150.2 (2006), pp. 267–269.

[97] Roza Vaez-ghaemi, Ashraf Hatamian-zaremi, and Thomas J Webster. "A review of fibrin and fibrin composites for bone tissue engineering". In: (2017), pp. 4937–4961.

[98] Johannes M. Van Noort. "Role of inflammatory mediators in autoimmune disease". In: *Thyroid Eye Disease: Diagnosis and Treatment* 300.3 (2002), pp. 65–77. DOI: 10.3109/9780203908983-9.

[99] Hideo Wada. "Disseminated intravascular coagulation". In: *Clinica Chimica Acta* 344.1-2 (2004), pp. 13–21. ISSN: 00098981. DOI: 10.1016/j.cccn.2004.02.015.

[100] Hideo Wada, Takeshi Matsumoto, and Tuyoshi Hatada. "Diagnostic criteria and laboratory tests for disseminated intravascular coagulation". In: *Expert Review of Hematology* (2012). DOI: 10.1586/ehm.12.57.

[101] Hideo Wada et al. "Comparison of Diagnostic Criteria for Disseminated Intravascular Coagulation (DIC): Diagnostic Criteria of the International Society of Thrombosis and Hemostasis (ISTH) and of the Japanese Ministry of Health and Welfare for Overt DIC". In: 22.September 2002 (2003), pp. 17–22. DOI: 10.1002/ajh.10377.

[102] Hideo Wada et al. "Disseminated intravascular coagulation: Testing and diagnosis". In: *Clinica Chimica Acta* 436 (2014), pp. 130–134. ISSN: 18733492. DOI: 10.1016/j.cca.2014.04.020. URL: http://dx.doi.org/10.1016/j.cca.2014.04.020.

[103] Hideo Wada et al. "Hemostatic molecular markers before the onset of disseminated intravascular coagulation". In: *American Journal of Hematology* 60.4 (1999), pp. 273–278. ISSN: 03618609. DOI: 10.1002/(SICI)1096-8652(199904)60:4<273::AID-AJH4>3.0.CO;2-N.

[104] Hideo Wada et al. "Increased Soluble Fibrin in Plasma of Patients with Disseminated Intravascular Coagulation". In: *Clinical and Applied Thrombosis/Hemostasis* 9.3 (2003), pp. 233–240. DOI: 10.1177/107602960300900308.

[105] Hideo Wada et al. "Modified non-overt DIC diagnostic criteria predict the early phase of overt-DIC". In: June (2010), pp. 691–694. DOI: 10.1002/ajh.21783.

[106] Manzhi Wang et al. "Retrospective evaluation of new Chinese diagnostic scoring system for disseminated intravascular coagulation". In: *PLoS ONE* 10.6 (2015), pp. 1–13. ISSN: 19326203. DOI: 10.1371/journal.pone.0129170.

[107] Masamitsu Yanada et al. "Disseminated intravascular coagulation in acute leukemia: clinical and laboratory features at presentation". In: *European Journal of Haematology* 77.4 (2006), pp. 282–287. DOI: 10.1111/j.1600-0609.2006.00711.x. eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1600-0609.2006.00711.x. URL: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1600-0609.2006.00711.x.

[108] Yun Zhang et al. "Aortic aneurysm and chronic disseminated intravascular coagulation: a retrospective study of 235 patients". In: *Frontiers of Medicine* 11.1 (2017), pp. 62–67. ISSN: 20950225. DOI: 10.1007/s11684-017-0498-7.