UNIVERSITÀ DEGLI STUDI DI TORINO

TIME TRIAL

Is **TI**me from ad**M**ission to surg**E**ry an independent prognostic factor for survival of patients with gastro-intestinal perforation associated with septic shock?
(TIME-Trial)

A SICO, SIC, ACOI, SICE, SICUT, SICCR Italian Intersocietary retrospective/prospective observational study

Central PI: Prof. Maurizio DEGIULI
Co-investigator and data-manager: Dr. Silvia SOFIA
Statistics and data analysis: Dr. Mariano TOMATIS

Azienda Sanitaria Ospedaliera S. Luigi Gonzaga Orbassano (To)

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An Italian intersocietary retrospective/prospective observational study

SICO	Prof M Degiuli, Central Principal Investigator
SIC	Dr M Zago: Co-PI
ACOI	Dr F Borghi: Co-PI
SICE	Prof G Anania: Co-PI
SICCR	Dr R Perinotti- Dr G Gallo : Co-PI
SICUT	Prof A Mingoli: Co-PI

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PRESENTAZIONE AI CONSIGLI DIRETTIVI

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DIFFUSIONE NELLE SOCIETA' E RACCOLTA ADESIONE DEI SOCI → Site-PI

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Azuhata *et al. Critical Care* 2014, **18**:R87
http://ccforum.com/content/18/3/R87

CRITICAL CARE

RESEARCH Open Access

Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock

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Abstract

Introduction: We developed a protocol to initiate surgical source control immediately after admission (early source control) and perform initial resuscitation using early goal-directed therapy (EGDT) for gastrointestinal (GI) perforation with associated septic shock. This study evaluated the relationship between the time from admission to initiation of surgery and the outcome of the protocol.

Methods: This examination is a prospective observational study and involved 154 patients of GI perforation with associated septic shock. We statistically analyzed the relationship between time to initiation of surgery and 60-day outcome, examined the change in 60-day outcome associated with each 2 hour delay in surgery initiation and determined a target time for 60-day survival.

Table 3 Comparison of survivors and non-survivors

	Bivariate model			Multivariate model		
	Survivors (n = 120)	Non-survivors (n = 34)	*P*-value	Odds ratio	95% CI	*P*-value
• **Patient background**						
Age, years, mean ± SD	64.3 ± 14.4	74.1 ± 8.7	0.0002*	0.95	0.88, 1.00	0.071
Male:female ratio	68:52	20:14	0.82			
• **Severity on admission, mean ± SD**						
SOFA score	8.5 ± 3.3	11.5 ± 4.3	<0.0001*	0.80	0.66, 0.95	0.014**
APACHE-II score	22.8 ± 8.5	28.1 ± 7.9	0.0014*	-	-	-
MOD score	4.3 ± 2.9	6.5 ± 3.7	0.0004*	-	-	-
Mean arterial pressure on admission, mm Hg	62.3 ± 29.5	62.2 ± 31.6	0.38			
Blood lactate concentration on admission, mmol/L	5.0 ± 3.6	8.1 ± 4.4	<0.0001*	0.88	0.77, 1.01	0.078
$ScvO_2$ on admission, %	60.8 ± 11.8	52.2 ± 12.1	0.0003*	1.04	0.99, 1.09	0.13
• **Surgery**						
Time from admission to initiation of surgery, hours, mean ± SD	2.6 ± 1.0	4.6 ± 1.6	<0.0001*	0.29	0.16 – 0.47	<0.0001**
Duration of surgery, hours, mean ± SD	3.4 ± 1.4	3.4 ± 1.4	0.92			
Patients needing re-laparotomy[##], number (%)	13 (10.8)	5 (14.7)	0.54			
Patients needing open abdominal technique, number (%)	1 (0.8)	1 (2.9)	0.33			

*P-value <0.2 **P-value <0.05

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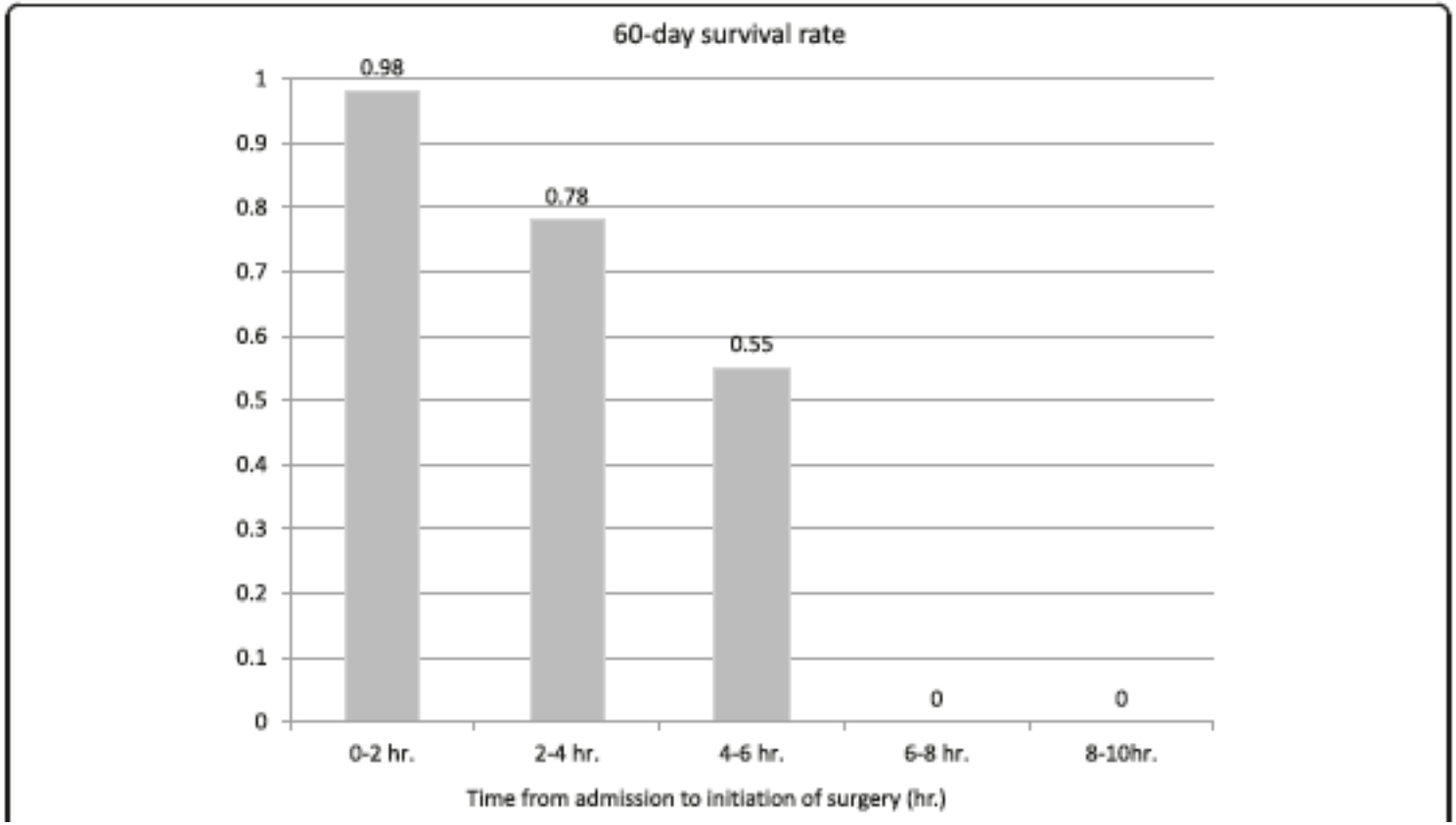

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Conclusion

Within several limitations, we conclude that time from admission to initiation of surgery for source control is a critical determinant of survival in patients with GI perforation with associated septic shock, under the condition that patients were treated with the support of early hemodynamic stabilization by EGDT. The target time for a favorable outcome may be less than 6 hours from admission. To improve the outcome of patients, we should not delay surgical source control procedures assisted by EGDT if patients have the complication of septic shock.

Background

International Guide-lines

2013 World Society of Emergency Surgery: "a surgical source-control has to be performed as soon as possibile"

Current literature PubMed

Heterogeneous patient populations
Different endpoints
Disagreeing data

Significant association between surgical delay and outcome

- **Azuhata 2014 (**154 pts) time to initiation of surgery (hours) was significantly associated with 60-day outcome (Odds ratio (OR), 0.31; 95% Confidence intervals), 0.19-0.45; P<0.0001)
- **Buck 2013**: (2668 pt) 2.4% decreased survival every hour of surgical delay in perforated gastric peptic ulcers
- **Zaid 2016** (8397 pt) increased LOS and health costs. More complications in elder population
- **Ong 2015** (144 pt > 60 y): Delays in surgery more than 24 h led to higher complication rates at 38.9% (P = 0.003)

Non-significant association between surgical delay and outcome

- **Hecker 2015**:((76 pts with SS) non-significant results
- **Vester-Andersen 2016, 2803 pts,** non-significant results

Aim of the study

- to assess the impact of surgical timing on
    - **60**-d mortality rate
    - Clavien-Dindo grade of postoperative complications

after surgery for gastrointestinal perforations **with** and **without** septic shock.

- to define the time threshold within which surgery can change patients' survival.

Definition of sepsis (retrospective study)

1) Infection documented or suspected and
2) an increase of 2 or more in *the SOFA score*

Definition of sepsis (prospective study)

1) Infection documented or suspected and
2) an increase of 2 or more in *the SOFA (Sequential Organ Failure Assessment) score*

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Definition of septic shock

- the association of clinical sepsis to
- persistent hypotension needing vasopressors to maintain a Mean Arterial Pressure (MAP) of 65 mmHg, after an adequate volume resuscitation
- serum values of lactates > 18 mg/dL (or 2 mmol/L)

Synchronous Treatment of associated sepitc shock

Early goal-directed therapy (EGDT

a procedure for the initial resuscitation of patients with septic shock that specifies **targets** to be reached within 6 hours of admission

It is appreciated that EGDT can speedily improve the circulatory dynamics and in-hospital mortality of patients with septic shock

- MAP > 65mmHg
- $ScvO^2$ >70%
- CVP 8 – 12 mmHg

Methods

Inclusion Criteria

Patients accessing Emergency Dept for gastro-intestinal tract perforations requiring surgery

With or without Septic Schock

Emergency surgery

Time period of Retrospective Study: 2010-2019

Time period of Prospective study:
IRB approval - Dec 2022

Exclusion Criteria

Patients < 18 years old

Non-operative management (NOM)

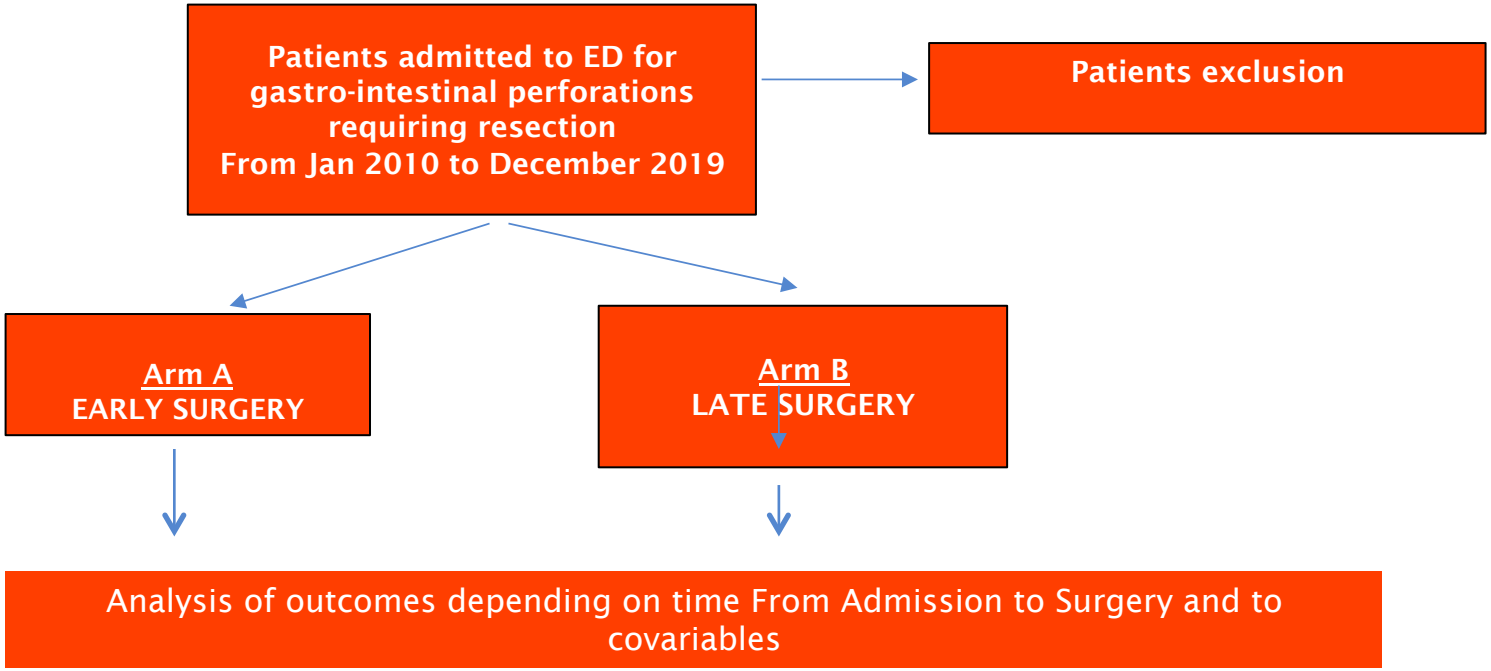
Covered Perforations only at CT scan

Perivisceral free air bubbles only at CT scan

Delayed surgery

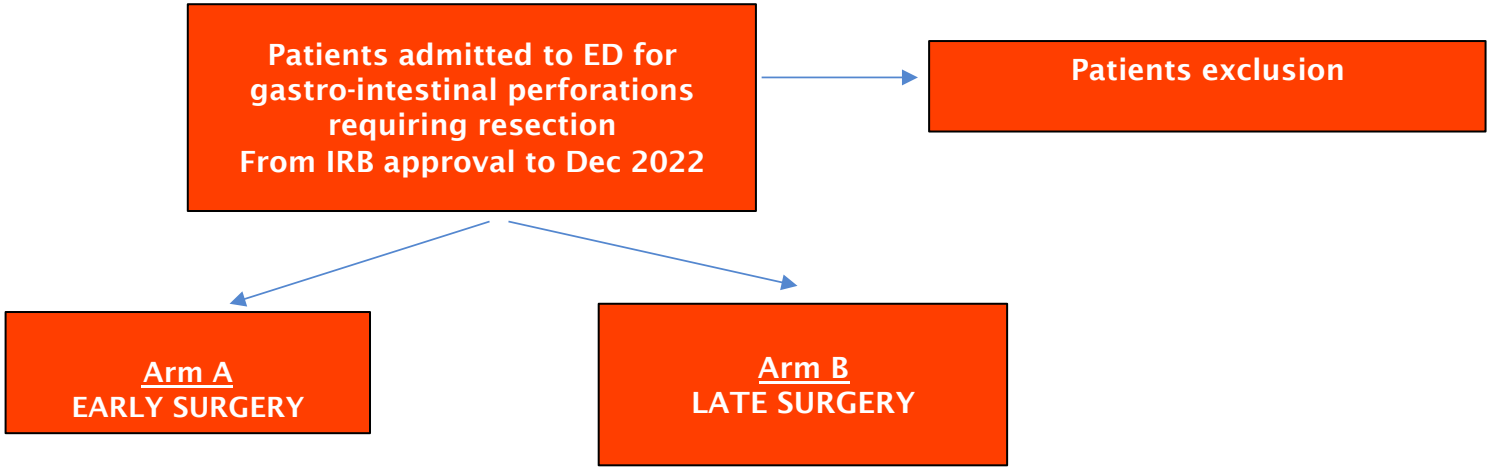
Methods

Design of the Retrospective Study



Methods

Design of the Prospective Study



Analysis of outcomes depending on time From Admission to Surgery and to covariables

Methods

Primary End-point

Clavien-Dindo $\geq$ 3

Secondary End-point

60-d mortality
Length of stay (LOS)
Intensive Care Unite (ICU)
Mechanical ventilation days
Re-intervention rate
30-d readmission rate

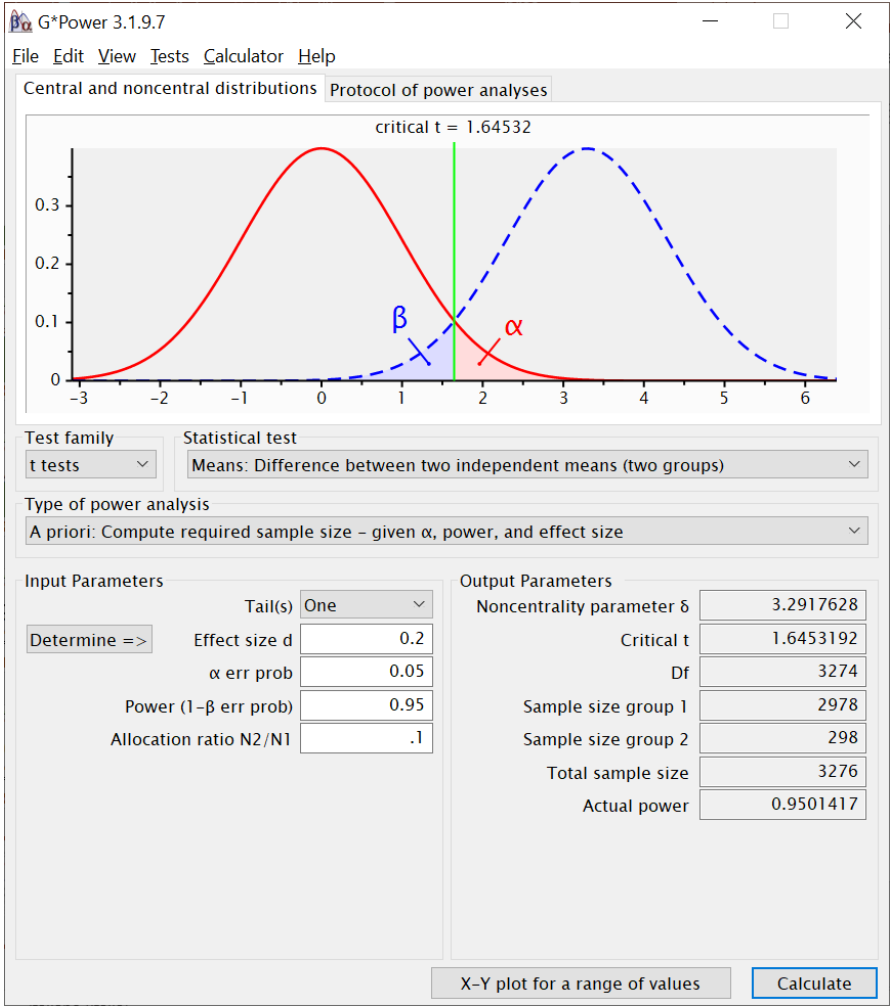
Sample size

N=3276

Early vs. Late

298 vs. 2978

10% vs. 90%



Methods

Variables examined

1 **Hospital characteristics**

teaching/non-teaching setting
I/II level ED
emergency surgery/volume x year
24H/on-call radiologist and surgical team
dedicated OR in ED

2 **Patients' background**

Gender, age, ASA, BMI
Medical history

3 **Management in ED**

admission date and time
Priority code at admission
Time of abdominal X-Ray and CT-scan
Time of request of surgical evaluation
Time of pt evaluation by surgeon on-call
Preoperative resuscitation management (Y/N, type, time of beginning)
Signs of sepsis (infection + qSOFA>=2) and shock
MPI, ESS and ACS NSQIP® Surgical Risk scale

CT-scan report

4 **Surgery**

Time of skin incision
Type, duration of surgery
Damage control surgery, Open Abdomen technique , surgical approach
Site and cause of perforation
Pathology

5 **Postopertive Course**

preoperative mortality
60-d mortality
total LOS
LOS in ICU, days of Mechanical Ventilation
Medical and Surgical complications (Clavien-Dindo)
Re-intervention rate
30-d Readmission rate

Methods

Scores
All participating centers will fill-out scores with clinical and laboratoristic findings with the aim to stratify patients according to clinical severity at admission in Emergency Department:

Sequential Organ Failure Assessment (SOFA)

Emergency Surgery score (ESS)

Mannheim Peritonitis Index

The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP®) Surgical Risk Calculator (ASS) [11]: https://riskcalculator.facs.org/RiskCalculator/

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TIMING

Retrospective phase
Data entry 2010/2019

March/April 2021 Deadline of retrospective data collection

June-July 2021
First Analysis
1st manuscript submission

Prospective phase (starting soon after IRB approval)

Dec 2022: Deadline of prospective data collection

April-May 2023:
Second Analysis
2nd Manuscript Submission

Coordinated by the University of Turin, Department of Oncology; Surgical Oncology and Digestive Surgery, San Luigi University Hospital– Orbassano (TO)

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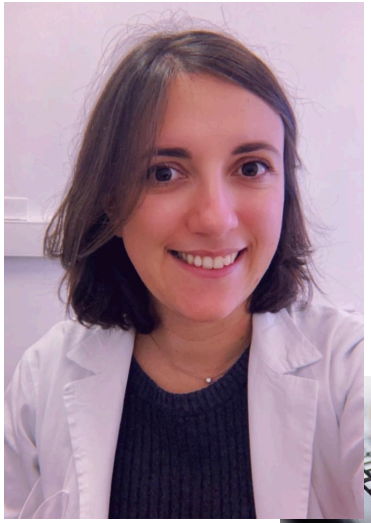
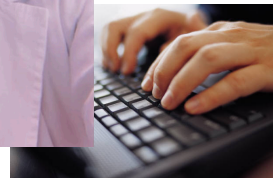
Silvia Sofia, MD





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